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October, 1913
University of Pennsylvania

A TEXTBOOK

OF

PHARMACOLOGY

AND

THERAPEUTICS

OR THE

ACTION OF DRUGS IN HEALTH AND DISEASE

BY

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FIFTH EDITION, THOROUGHLY REVISED

ILLUSTRATED WITH SIXTY-ONE ENGRAVINGS

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PREFACE TO THE FIFTH EDITION.

The progress of the subject in the last few years having necessitated changes in a number of chapters of the textbook, the opportunity has been taken to revise the whole thoroughly. The amount and importance of the researches published in these years testifies to the growing interest in the action of drugs and their application, and to the abandonment of the nihilistic attitude towards therapeutics, which was formerly so discouraging. On the experimental side, many authorities evince a tendency to base the effects of drugs more on their physical characters and less on their chemical combinations than formerly, and I have attempted to present this view as far as it is satisfactorily established, while avoiding its adoption as the sole principle underlying pharmacological action. Important advances have been made in the study of many individual drugs, such as adrenaline and ergot, permitting of a more definite statement of their action. In therapeutics, new methods of clinical examination have thrown much light on the use of several remedies, such as digitalis; and the study of trypanosomiasis and other protozoal infections has suggested new points of view in regard to the specific remedies, such as arsenic and mercury. Space has been found for a short chapter on the antitoxins and their uses, but no attempt has been made to follow the mazes of theory in which this subject has become involved. There is a notable ebb in the flood of new remedies which threatened to submerge medicine in the end of last century, and the use of many of the minor older remedies is also declining, so that I have been able to curtail the discussion of many of them and to discard some altogether. The tendency of modern therapeutics is to abandon many of these untrustworthy or feeble remedies and to depend on those of which the efficacy and power are beyond question.

A. R. C.

LONDON, 1910.

PREFACE TO THE FIRST EDITION.

THE following pages were written to supply a want which I have felt keenly in teaching the subject of pharmacology to students who have completed the purely scientific branches of medicine and are beginning their clinical studies. My object has been to bridge over the hiatus which exists between the phenomena occurring in the normal organism and those which are elicited in the therapeutic use of drugs, to show how far the clinical effects of remedies may be explained by their action on the normal body, and how these may in turn be correlated with physiological phenomena. It necessarily follows that the subject is treated from the experimental standpoint, and that the results of the laboratory investigator are made the basis of almost every statement. Where these fail to elucidate the therapeutic effects or even to suggest a possible explanation, I have preferred to leave the question undiscussed rather than to call on such occult *dei ex machina* as alterative or tonic actions.

Two great difficulties present themselves at the outset to the writer on pharmacology who is not satisfied to take his statements at second hand, or to formulate explanations from his unaided inner consciousness; these are the overwhelming literature on the subject, and the wide limits of the field of study. As regards the first, I have read, as far as was in my power, the original papers of importance, and in order to facilitate the work of others who may wish to follow this, the only satisfactory method of study, have appended a bibilography to each chapter. It was impossible within the limits of a textbook to make this complete, or even to enumerate more than a few of the works consulted, and I have accordingly selected those which appeared most important, and those which were furnished with the most complete bibliography.

As regards the scope of the work, I have attempted to give the present standpoint of knowledge of such bodies as are of therapeiutc or toxicological interest, and also of those which, possessing in themselves no immediate interest in practical medicine, have thrown important light on biological problems, and are accordingly likely to be referred to inscientific literature.

Unfortunately, a writer on this subject cannot as yet restrict his attention to these classes, but must refer at more or less length to many drugs which possess little interest either from a therapeutic or a scientific point of view. It is true that the more advanced teachers of medicine have very properly abbreviated their lists of remedies, until those generally employed may be enumerated in units where they were once counted in scores, but the student on going into practice meets numbers of drugs previously unknown to him, and not appreciating that these have already been tried and discarded by his teachers, is tempted to fall into the slough of unreasoning empiricism. There is still a tendency even among the educated to ascribe therapeutic virtues to every new weed and every new product of chemical industry, and the teacher of pharmacology must not only point out the good, but has the more ungrateful task of condemning the worthless. The period of constructive pharmacology has scarcely dawned; at present its chief function is destructive and critical.

In dealing with each drug, I have attempted to unify the whole action by using the most distinctive feature as a centre around which to group the less important symptoms. Where, as is often the case, there is a divergence of views among authorities, I have generally presented only one side of the question, except in very important subjects. This dogmatic method has of course its drawbacks, but is, I think, preferable to involving the student in a labyrinth of arguments and counter-arguments, the respective weight of which he is quite unable to estimate.

The preparations enumerated are those included in the United States and the British Pharmacopœias, and such others as seemed of sufficient importance. I have attempted to indicate by special type (small capitals) those that are more generally used.

Some explanation may seem necessary for the introduction of the word "therapeutics" in the title, in view of the fact that pharmacology is stated in the introduction to embrace all that part of therapeutics which can be treated of apart from clinical lectures. This definition is not universally used, however, and it has been felt advisable to indicate more distinctly the scope of the work by adding the more familiar term.

To those acquainted with the *Grundriss der Arzneimittellehre* of Schmiedeberg, it is unnecessary to state that this volume has been largely inspired by that classical work. Some chapters may in fact be regarded as merely expansions of those issued from the Strassburg laboratory, but this must necessarily be the case in any work which pretends to treat the subject from the experimental standpoint. The use of such a model naturally exposes the writer to the criticism that he has fallen short of the original standard, especially when such divergences are made from it as occur in this work. But if I have departed from the letter in some respects, I hope that at least the spirit of the *Grundriss* has been preserved in these pages. I must acknowledge my indebtedness for references to papers which might have otherwise escaped my notice to the following textbooks: Kobert's *Lehrbuch der Intoxicationen,* Lewin's *Nebenwirkungen der Arzneimittel,* Husemann's *Pflanzenstoffe,* Harnack's *Arzneimittellehre,* H. C. Wood's *Therapeutics, its Principles and Practices* and Stokvis' *Leçons de Pharmacotherapie.*

Finally, I have much pleasure in acknowledging the assistance of my colleagues in the preparation of this work, particularly that of Professor Huber, who furnished several of the illustrations. Dr. G. B. Wallace has put me under lasting obligations through the patience and care which he has bestowed on the tedious task of proof-correction, and I must thank Dr. W. Mogk also for his assistance in this part of the work.

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A TEXT BOOK OF PHARMACOLOGY.

INTRODUCTION.

Pharmacology is the study of the changes induced in living organisms by the administration in a state of minute division of such unorganized substances as do not act merely as foods. Many of the best known of these substances are used to counteract the effects of disease, or to reinforce the tissues in their struggle to maintain their functions, when these are rendered abnormal. These substances are known as *drugs*, and the art of applying drugs in disease is *Therapeutics*. Other substances are of little or no value in disease, but are of importance because they act as *poisons*, that is, cause dangerous or fatal symptoms in man or animals, when they are ingested in quantity. The practical study of the effects of these poisons in man—the diagnosis and the treatment of poisoning, and the methods of detecting the poison—is termed *Toxicology*. But the explanation of the symptoms induced by chemical substances, and their study, as apart from their practical applications, belong to the field of pharmacology, which includes not only the effects of drugs and poisons, but those of any substance which induces changes in the living organism, whether those changes are of benefit to it, injurious, or indifferent.[1]

The substances must, of course, conform to the requirements of the definition. Thus, a needle introduced into the tissues induces effects which are outside the field of pharmacological investigation, because it is not in a state of minute division. But the iron of the needle may be reduced to a fine powder and induce changes in the body which are then the legitimate subject of research. Similarly the drug must be introduced from without, for many active agents are formed within the body, but their study belongs rather to the departments of physiology and pathology; and the effects of organized bodies introduced from without are now studied under bacteriology. Pharmacology is really a department of biology, very closely related to the other sciences included by that term. Thus, as physiology is the study of the life of the normal organism, pharmacology is the study of the organism rendered abnormal by drugs, while in pathology the phenomena of life under disease are examined. All three subjects may be pursued without reference to the practical needs of medicine, and all three are closely interconnected and mutually dependent, for, in many instances, the normal condition of an organ can be recognized only by considering the results of its destruction by disease (pathology), or of its paralysis or stimulation by chemical agents (pharmacology). Similarly, many of the features of disease are now recognized to be due to the presence of unorganized poisons formed in and by the tissues, and it accordingly becomes difficult to accurately define the limits of pathology and pharmacology.

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[1] It is quite impossible to distinguish between drugs and poisons. Almost all remedies given in excess cause dangerous or fatal symptoms, while many poisons are valuable remedies in small doses. Some bodies may in fact be remedies, foods, or poisons according to the quantity ingested and the method of application.

Even when these limitations are accepted, pharmacology has an enormous field to cover, and one which has been only very partially explored at the present day, in spite of the unremitting industry of many investigators. But a small part of the subject has been sufficiently developed to admit of text-book treatment, that namely, which is concerned with drugs used in therapeutics and with the commoner poisons. The slow advance of pharmacology is partly due to its position midway between the biological sciences and practical therapeutics, for while the biologist confounds it with clinical study, the clinician regards it as an experimental science. Its relation to biology has already been mentioned and its relation to practical therapeutics is no less close, for the effects of drugs in disease are as much a part of pharmacology as is their action in the normal organism. The aims of the pharmacologist and the clinician are not identical, however. The former seeks to solve the problem how the drug acts in a given case, while the primary object of the latter is to remedy the condition by any means in his power. Thus, in a case of heart weakness, the clinician prescribes some remedy which he has found of benefit in other similar cases, and regards only as of secondary interest the question which to the pharmacologist is the absorbing one, namely, whether the drug acts on the heart directly or through some other organ. Of course the results are of mutual advantage, for the physician supplies the experimental investigator with new facts and with new fields of inquiry, while the latter may indicate more exactly the conditions in which the drug is likely to be of benefit in the future by defining the method in which it acts. It is, therefore, much to be regretted that differences of opinion so often arise between these two classes of observers, for these can only retard the progress of both the science and the practical art. Doubtless there are often faults on both sides. The scientist sometimes insists too strongly on inductions drawn from a limited number of animal experiments, and refuses to admit results which have been obtained in thousands of cases of disease by competent observers. On the other hand, the therapeutist often lays too little weight on the general principles governing the interaction of the drug and the organism. Both often exceed the limits of their provinces, the scientist in refusing to admit effects of which he has perforce but a small experience, the clinician in attempting to refute deductions founded on experiments which he has no opportunity of performing. An example may render the relation of these allied subjects clearer, and one has been recently offered in the discussion regarding the effects of iron. This metal has been used for many years in a form of anæmia, and its curative properties are attested by many thousands of cases and by whole generations of practical physicians. A pharmacologist, therefore, exceeds his province when he expresses doubt regarding this clinical fact simply because

Materia Medica or Pharmacognosy = study of botanical + chem. propertie
Pharmacy — study of preparation

he is unable to explain it, but he is within his rights in discussing the means by which iron acts as a remedy. The clinician, on the other hand, enters on a pharmacological question when he attempts to determine whether iron acts by absorption or by its presence in the bowel, and must base his arguments on scientific experiment and not on his clinical experience of the curative effects of the metal. Fortunately for the progress of medicine and pharmacology, the scientific clinician is imbued with the desire to ascertain the methods in which drugs act as well as to cure disease, and thus unites clinical observation with pharmacological research. It is to be anticipated that the results of the practical physician and of the experimental investigator will come into more complete accord as more exact methods of clinical research are used by the former, and a wider laboratory experience is attained by the latter. But both methods are necessary to the complete knowledge of the action of a drug. Animal experiment cannot be dispensed with, for only thus can the action of drugs be ascertained in detail and expeditiously, and at the present time, when a new remedy appears almost every week, it is impossible to await the verdict of the clinics to separate the useful from the worthless, even if it were permissible to apply to the human subject drugs of unknown action and potency.

Pharmacology is one of the most recent developments of medical and biological science. It is true that from the earliest times attempts have been made to explain the effects of drugs on the then prevailing theories of pathology, but the objective study of the action of drugs on the organism has been a development of the nineteenth century, or it might almost be said, of the second half of it. During this period the same methods of research have been adopted as had earlier proved so fruitful in physiology and pathology, and with equally happy results. The study of drugs was termed *Materia Medica* up to this time, and comprised an examination of their botanical and chemical properties along with some account of the diseases in which they had proved of value. This descriptive rather than experimental study has been continued under the name of *Pharmacognosy,* but is now pursued by pharmacists chiefly. Undoubtedly the student of medicine ought to know those characters of drugs which are of importance as modifying their action and application, but it is undesirable that his valuable time should be occupied in the detailed description of crude substances, which he may probably never have an opportunity of seeing in his future practice.

Another subject which now occupies a much less prominent position in medical study than formerly, is *Pharmacy,* or the art of preparing drugs for therapeutic use. Some general knowledge of the methods used is no doubt indispensable to the educated physician, but the details may be left to the pharmacist. Pharmacy will probably occupy a still more subordinate position in medical education as the tendency to include only one or two drugs in a prescription becomes more widespread. As long as a dozen or more components went to

Action: physical, chem. - more often adsorption (affecting cell physically rather than chem.). Eff. conc. of drugs may alter rate of exchange between fluids & cells.

make one mixture, it was of importance to know their solubility and their interactions, but with the decay of the complex prescription the study of pharmacy by medical students has certainly become less imperative.

MODE OF ACTION OF DRUGS. STIMULATION, DEPRESSION AND IRRITATION.

A number of drugs affect the organism only through their obvious *physical* properties, as when an inert oily body is applied to an abraded surface and promotes its healing by protecting it from irritation and from the evaporation of fluid, or when common salt absorbed into the blood changes its osmotic tension, and thus alters the distribution of fluids in the tissues. On the other hand, many effects are due to simple *chemical* reactions; for instance, bicarbonate of potassium may be used to neutralize the hydrochloric acid of the gastric juice, just as it combines with acid in a test-tube, and many of the effects of oxalates arise from their forming insoluble salts with the calcium of the tissues. In the great majority of drug actions, however, no such simple relations obtain, and it is still a question whether definite chemical combinations occur with the living tissues or whether the effects arise from the formation of such loose connections with the protoplasm as have been termed "adsorption compounds"; an illustration of these is offered in the combination of dyes and fibres. In recent years these adsorption phenomena and others in the borderland of physics and chemistry have received much attention, and the application of the results of these investigations to pharmacology has proved of great value already and promises to elucidate in the future many problems which have hitherto been unapproachable. Examples of such applications will be met in the Meyer-Overton theory of narcosis and in the chapters on salt action. The tendency of study in this direction is to reduce the class of reactions which have hitherto been ascribed to special chemical affinity between drugs and protoplasm, and to attribute many of the changes induced by drugs to the physical structure of the living cell rather than to its chemical constitution.

Unless a drug can penetrate into a living cell, it can only influence it by altering the rate of exchange of water and other permeating substances between the cell and the surrounding fluid, and the degree of alteration depends on the concentration of the drug (see salt action). If, on the other hand, it can penetrate the cell, its effect is determined by the amount of the drug with which the cell comes in contact, that is, again, with the concentration relative to the cell mass. Thus it has been shown that a very dilute solution of mercury salts may prove poisonous to a few bacteria because the metal accumulates in them, while if more bacteria are present in the solution it may be harmless to them because it is distributed through a larger amount of living matter. As the accumulation proceeds, the action becomes more intense, and from this it may be inferred that the cell contents com-

Certain cells specific for certain drugs. Passage of drug thru cell wa may determine action rather than its chem. comb. or adsorption in the cell. Drugs affect functions of organs quantitatively and not qualitatively. Stimulation & depression have reference to specialized function. Irritation to vital properties.

bine with the poison either chemically or by adsorption and that the progressive toxic action is due to the normal constituents of the cell becoming less in amount, while the altered contents increase. In short, the action is precisely similar to that occurring between two chemicals in solution in the test-tube or to the coloration of a fibre by a dye. In some instances, however, Straub states that the action does not progress with the amount of poison in the interior of the cell, but with the rate of permeation. Thus he found that a cell exposed to certain poisons was affected as they permeated into it, but recovered as soon as the actual movement of the molecules into the cell ceased, although it now contained much more of the poison than was present at the time at which the action was marked.

Different cells absorb different poisons and this explains in part why drugs act on one organ and not on another; for example, why strychnine acts on the spinal cord and not on the heart. But even when a poison penetrates into a cell it may not injure it although other cells are immediately destroyed by it. There are thus other factors in the action of drugs besides those that determine penetration, and of these nothing is known at present.

When a cell is affected by a poison, the extent of its activity is changed but not the kind. The reflex movements may be augmented under strychnine or may be lessened under chloral, but they remain reflex and cannot under any circumstances partake of the nature of voluntary movements. In other words, the effects of drugs are quantitative, not qualitative, the activity of living matter may be changed, but the form which the activity assumes is unchangeable.

Drugs which increase the activity of any organ or function are said to *stimulate* it, while those which lessen the activity are said to *depress* it. Another condition induced by drugs is *irritation,* for although this term is often applied loosely as a synonym for stimulation, the two conditions are not identical. Stimulation is properly used to indicate an increase in the specialized function of a cell, producing, for instance, in the spinal cord an increase in the reflex excitability. Irritation, on the other hand, is used rather in reference to the changes in the conditions common to all forms of living matter, that is, it indicates a change in the nutrition and growth of the cell, rather than in the specialized functions. Irritation may thus be induced in all kinds of tissues and is the commonest change caused by drugs in the less differentiated forms, such as the connective tissues and ordinary epithelia; while stimulation is met with in the more highly specialized cells, such as those of the heart, nervous system, or secretory glands. In many instances the irritant action of drugs may be explained by their known reactions with the proteids of the cell; for example, substances which dissolve proteids, or precipitate them, or withdraw fluid from them, all tend to cause irritation when they are applied to living tissues. In other cases irritation appears to be induced through some chemical action the nature of which is quite unknown.

When stimulation is prolonged or excessive, the protoplasm generally becomes depressed and finally loses its activity entirely (paralysis). Some authorities have asserted that depression is invariably preceded by stimulation, and that stimulation sufficiently prolonged invariably leads to depression and paralysis. Both statements are too absolute, although they are true in the great majority of cases. For example, the action of atropine on the terminations of the cardiac inhibitory nerves is purely depressant. Even the most minute quantities of this alkaloid never increase the activity of these terminations, for if a quantity too small to paralyze them is ingested, it has apparently no effects whatever, and as the dose is increased, the first effect is paralysis.

Depression, whether induced directly, or following on stimulation, has been shown in several instances to resemble the fatigue induced by the prolonged exercise of the normal organ, and it is probably true that depression and fatigue are, in all instances, identical in appearance, although not necessarily identical in cause. For example, the phenomena of fatigue of the terminations of the motor nerves in muscle resemble exactly those induced by curara, but in the former the cause may be that the conducting substance of the nerve ends has been used up by the repeated passage of impulses, while in the latter the conducting substance is so changed that it becomes incapable of transmitting stimuli to the muscles. The final result is, of course, the same; there being no available conducting substance, impulses fail to reach the muscle. But the fatigued terminations rapidly recover, as conducting substance is reformed, while the curarized recover only when the poison is eliminated.

In most cases an excessive dose of a stimulating poison leads to depression and paralysis. The cell becomes functionally dead, but if the failure of its function does not involve the death of the organism, it may recover and reassume its ordinary function as if no stage of inactivity had intervened. Excessive irritation, on the other hand, leads to actual death and disintegration, from which there is no recovery. For example, the cells of the spinal cord are first stimulated, and later paralyzed by a large dose of strychnine, but this is not fatal to cold-blooded animals, and after a few days the spinal cord regains its normal function, as the poison is eliminated. On the other hand, the injection of an irritant into the subcutaneous tissues causes dilatation of the vessels, effusion of fluid, and increased growth and rapid division of the cells. If only a small quantity be injected, this condition is recovered from, although it generally leaves evidence of its presence in the form of an increase in the fibrous tissue. But if the irritation be intense, the cells undergo degeneration and die, and an abscess is formed. The cells thus destroyed can never recover as the paralyzed ones do. They are either absorbed, or removed by the opening of the abscess, and their room is filled by the overgrowth of the neighboring tissues.

Drugs (most) have specific action, not dependent on quantity. Of general action termed "protoplasm poisons" (yet specific if into circulation)

ELECTIVE AFFINITY OF DRUGS. PROTOPLASM POISONS.

Most drugs have an elective affinity for certain definite tissues. Thus, some attack the heart only, others the central nervous system and others the terminations of the motor nerves in muscle. Among the cardiac poisons again, some act on the ventricle, others on the auricle, and among the poisons of the central nervous system, some act primarily on the cortex, others on the medulla oblongata and others on the spinal cord. This elective affinity is not merely a question of degree, as is sometimes stated, for a drug which has a powerful action on the brain may have no effect on the heart except when administered in such quantities as alter the physical characters of the blood. A drug may even alter different structures in diametrically opposite directions. Thus, atropine depresses certain nerve terminations, but stimulates the brain, and curara, which paralyzes the peripheral terminations of the motor nerves, stimulates the spinal cord. In some instances the immunity of a cell to the action of a drug may perhaps be explained by the latter failing to penetrate into its interior, but this is not true in all cases.

The fields of activity of different drugs vary greatly in extent. One may comprise only the terminations of the secretory fibres in the sweat glands (agaricin), while another, which affects these in the same way, may involve many other terminations in its action (atropine). Most poisons, however, while acting on a certain narrow area in small doses, extend the limits of their activity when larger quantities are ingested. Thus, a poison which acts in small doses on the medulla oblongata only, may, when exhibited in larger quantities, involve the spinal cord and the brain, and in still greater concentration may affect the heart and other organs. No poison is known that acts equally on all organs and tissues, but those which have a wide field of operation are often known as *protoplasm poisons*. These paralyze any form of living matter when they are brought in contact with it in sufficient quantity, but if they are injected into the blood and thus distributed equally throughout the body, they invariably select some special organ as the chief seat of their activity. This is exactly parallel to the behavior of chemical agents in the laboratory. For example, acetate of lead added to a solution of a chloride, or of a sulphate, precipitates it, but added to a mixture of the two, throws down more of the sulphate than of the chloride. Nitrate of silver, on the other hand, precipitates the chloride only. Acetate of lead may be compared to the protoplasm poisons, nitrate of silver to those with a less extensive field of action. As protoplasm poisons affect a large number of different forms of living matter it follows that they alter the nutrition rather than specialized functions. Many of them cause irritation; others are used to destroy or retard the growth of microbes and are known as disinfectants or antiseptics.

Local action = action before absorption. General = selective action after absorption into circulation

REMOTE, LOCAL, AND GENERAL ACTION.

Drugs change directly only those organs and tissues with which they come into immediate contact. But the alteration of one part of the organism very often entails that of another to which the drug may not have access, or for which it has no special affinity, because impulses are transmitted through the nerves, or changes are induced in the circulation and nutrition. Thus irritation of the skin may alter the rate of the pulse by impressions being transmitted by the cutaneous nerves and reflected along the inhibitory nerves of the heart. Similarly a poison that weakens the heart may induce disorder of the respiration, from the circulation being deficient in the medulla oblongata; and depression of the brain may lessen the oxidation in the muscles, because it leads to lessened movement. These secondary changes, which are not due to the direct action of the drug on the organs concerned, are known as *remote* or *indirect* effects.

The *local* action of a drug is that induced at the point of application before it enters the circulation, the *general* or systemic action is that due to its elective affinity for certain organs to which it is carried by the blood. The local effects are very often entirely different in nature from the general action, for a drug may act as an irritant at the point of application and as a depressant to the brain when it is carried to it in the blood. Local effects may be induced wherever the drug can be applied—in the skin, the alimentary tract, the respiratory passages, and the other mucous membranes. They also occur in the subcutaneous tissues when the poison is injected hypodermically, and in any of the deeper organs and tissues which can be reached by the needle of the syringe. Local remedies may cause irritation, or may protect the surface from irritation, may depress the sensory end-organs and cause local anæsthesia, or lessen secretion, or alter the functions at the point of application in many other ways. They may also have remote effects, as has been mentioned. Many drugs have only a local action, because they are not absorbed, are absorbed in inactive forms, or are excreted or deposited as rapidly as they pass into the circulation, so that enough is not present in the blood at any one time to induce general effects. On the other hand, many powerful poisons have little or no effect at the point of application, but possess an elective affinity only for some organ to which they are carried by the circulation.

THE RELATION BETWEEN CHEMICAL COMPOSITION AND PHARMACOLOGICAL ACTION.

If the effects of drugs on living matter were due to a chemical reaction between them, it might be expected that those drugs which present a close resemblance in their chemical properties and composition would induce similar changes in the organism. And in a number of instances this has proved correct, and there has appeared to be a definite relation between pharmacological action and chemical composition. For example, so many members of the methane series of chem-

Only absorption depends on 1) solubility in fluids of tissues 2) volatility 3) diffusibility in colloidal sol.

istry depress the central nervous system that this may be regarded as a general property of these bodies, just as they possess certain general chemical reactions, which distinguish them from the members of other chemical series. In the same way, the heavy metals resemble each other in their general effects on the organism, just as they react similarly to some chemical tests. But whenever an attempt is made to follow this relation in detail, the analogy breaks down, because factors which it is impossible to deduce from the chemical constitution make themselves felt. Exactly the same thing occurs in chemistry; for example, the heavy metals resemble each other in so many respects that it might be inferred that the sulphides would be of the same color, or that the chlorides would be equally soluble in water, but experiment shows that this is not the case. In the same way they resemble each other in many points in their effects in the organism, but it cannot be inferred from this that they will have the same effect on any given organ or in any given respect. A simple example of the very different effects in the organism of drugs which are closely related chemically is offered by the action of the simpler members of the acetic acid series on the sense of smell. For formic, acetic, propionic, butyric and valerianic acids can be easily distinguished by their odors, that is, they act differently on the terminations of the olfactory nerves, yet they form a homologous series of as closely related members as any chemical series can offer. They present certain differences in their chemical reactions, of course; for example they vary considerably in the solubility of the salts they form with barium and calcium, and it is impossible to explain, or to anticipate these variations from any consideration of their chemical constitution. If then their reactions with such simple and familiar bodies as calcium and barium cannot be anticipated, it would seem futile to attempt to foretell their behavior towards the infinitely more complex and less known protoplasm of the nerve terminations.

As a matter of fact the physical properties of drugs appear to have a more direct bearing upon their action than the chemical structure; that is, the properties of the molecule as a whole determine its effects more than any of its constituent parts. For such properties as solubility in the fluids of the tissues, volatility and diffusibility in colloid solutions determine whether a drug can be absorbed and come into contact with the living cells; thus, if two drugs differ in solubility in water their effects may be very different, although they are nearly related chemically. These physical characters depend ultimately upon the chemical structure, but as yet little has been done to correlate them with it and it is impossible to deduce them from the structural formulæ.

A great deal of time and energy has been devoted to an attempt to bring the effects in the organism of certain metals (notably the alkalies) into relation with their atomic weights, their valency, electrical charges, and other properties, but no results are to be expected from these researches so long as the ordinary chemical reactions of these

Cond. a Variables for drug effect. Wt. age ($\frac{age}{age+12}$), Adm. present vomiting, diarrhoea, menstruation, pregnancy. Resistance in idiosyncrasy (rapid or delayed resorption). Congenital + acquired tolerance easily lost – cross tolerance. Cumulative effect. Synergist (adjuvant). Antagonist (drugs formed in disease). Path. cond.

bodies can only be formulated to a limited extent and imperfectly from such considerations. In particular, it seems of little interest to determine their exact relative toxicity, since there is no question that they do not all act on the same organs; and if one act on the brain and another on the heart, one by its specific affinity for an organ and another by inducing physical changes in the fluids of the body, these differences are sufficient to nullify any relation which they may bear to each other in regard to the exact fatal dose. As has been stated, it may be inferred with some probability that any substance belonging to certain wide chemical groups will induce symptoms in the organism resembling in general characters those of the other members, provided always that it does not contain some radicle which renders it inactive, or gives it a more powerful action in some other direction. But the details of its action can be ascertained only by actual experiment, exactly as the details of its chemical behavior can be known only by performing the necessary reactions; and as there is no prospect of explaining the latter from its constitution at the present time, there is still less hope that much advance will be made in the near future in formulating the laws governing the details of its pharmacological effects.

CONDITIONS MODIFYING THE EFFECTS OF DRUGS.

The effects of drugs on the living organism are subject to some modifications in certain individuals and under some conditions, which it is of importance that the physician should recognize, as the dose has to be altered when they are present. One of these is the **Size and Weight.** If the same amount of a poison be distributed through the tissues of a large individual as of a small one, less is contained in any given organ of the former and less effect is therefore observed. This has been ascertained chiefly in animal experiment, in which the effects of drugs can be estimated much more exactly than in man, but it undoubtedly holds good for human beings also. Very large individuals, then, require a somewhat larger dose than ordinary persons, while in treating individuals of small stature, the dose has to be reduced.

The **Age** of the patient has also to be taken into account in prescribing. Children ought to receive much smaller doses than adults. The more powerful action of drugs in children is due in part to their smaller size, in part to the more active growth of certain tissues and to the less complete development of others, such as the central nervous system. The dose for a child is generally calculated according to Young's formula, in which a fraction obtained by dividing the age by the age + 12, is taken as the proportion of the adult dose required. Thus, for a child of four years, the dose would be $\left(\frac{4}{4+12}=\right)$ ¼ of the adult dose, for one of one year $\left(\frac{1}{1+12}=\right)$ 1/13 of the adult dose.

According to another less used formula, the dose for a child is ascertained by dividing the adult dose by 20, and multiplying the result by the age. Brunton suggests dividing the dose by 25 and multiplying the result by the age at the next birthday. These formulæ are not, however, invariably safe guides to follow in prescribing. For example, the narcotics, particularly opium and its preparations, must be given during the first years of life in much smaller quantities than are indicated by Young's rule, while alcohol may be administered in comparatively large doses.

The usual dose advised has to be modified for children then, and may be taken as that suitable from 20–60 years. After this age is passed, it is again reduced somewhat, so that from 70–80 about ⅘ of the adult dose is advised, and after 85 it may be reduced to ½. There are exceptions to this rule also, large doses of the purgatives, for example, being often necessary in old people.

Sex.—Women generally require somewhat smaller doses than men, because of their smaller size, and it is often stated because their tissues react more strongly to some drugs, though this has not yet been satisfactorily established.

Temporary conditions also influence the activity of drugs. Thus, *after a meal*, a poison is absorbed more slowly from the stomach than when it is taken fasting, and any local irritant action is also less marked, because the drug is diluted by the contents of the stomach. *Irritation of the stomach and intestine* may also modify the effects of drugs; thus in some forms of dyspepsia the absorption is slower than usual and little effect may be induced by the ordinary dose, while irritant drugs naturally cause more disturbance of the digestion in these cases. On the other hand, a slight congestion of the stomach and bowel tends to promote absorption, and it has been found that more of a heavy metal is absorbed when it causes some destruction of the mucous membrane than when it is given in small quantities. Vomiting and diarrhœa, of course, tend to lessen the action of drugs by removing them rapidly from the alimentary canal.

During *pregnancy*, purgatives have to be used with great care, because they induce congestion of the pelvis, and may lead to abortion. Drugs acting on the uterus, or inducing a marked fall of blood pressure, are to be avoided because the former may cause the evacuation of the uterine contents, while the latter may lead to asphyxia of the fœtus. Many drugs pass from the mother to the child, and this is to be borne in mind, as quantities which are insufficient to poison the former may have more serious effects on the latter. During *lactation*, it is important to remember that active bodies may be excreted in the milk, and may either act on the child or render the milk distasteful to it. In *menstruation*, purgatives are to be avoided, as they tend to increase the flow, and all very active drugs are to be used with care or abandoned temporarily.

The **Time of Administration** has also some influence on the effects of drugs. The body is generally more resistant in the morning than in the evening, especially in the case of narcotic drugs; thus a dose of a soporific which may have little or no effect in the early hours, induces sound sleep when given in the evening, because the brain is already fatigued and depressed.

Idiosyncrasy is used to denote an unusual effect for which no explanation can be found. Some persons react more readily than usual to the ordinary dose, while in other instances, a much larger quantity can be taken without any effect. Others, again, show symptoms which are entirely different from, and which may, in fact, be diametrically opposite to those ordinarily observed. These idiosyncrasies are naturally more frequently seen, and are better known when they arise from widely used drugs. Thus the modern antipyretics have so often induced abnormal symptoms that these are well known, but it is not improbable that if other drugs had been used, or rather abused, to the same extent, they would be found to induce unusual reactions in an equally large number of individuals. An idiosyncrasy, as has been said, cannot be explained in the present state of knowledge, but some conditions which have been termed idiosyncrasies are probably due to abnormally rapid, or to retarded absorption or excretion. Idiosyncrasies are not confined to human beings, for not infrequently one animal reacts quite differently from others of the same species.

As has been mentioned, one form of idiosyncrasy consists in the failure of the individual to react to the ordinary dose of a drug. This is known as **Tolerance,** and this particular form of idiosyncrasy may be termed *congenital* tolerance. Certain species of animals tolerate quantities of drugs which would be fatal to others of the same size. In fact, so frequently is this the case that it is impossible to determine the fatal dose of any drug on an animal from experiments performed upon others of a different species, even though it be nearly related. One of the most remarkable examples of this form of tolerance is met with in the hedgehog, which resists large doses of many very active poisons. Another well-known example is the tolerance of the rabbit of large quantities of atropine.

A form of tolerance which is a matter of everyday observation is that induced by the prolonged use of a drug, which has been called *acquired* tolerance, or mithridatism, from the belief that Mithridates protected himself in this way from the danger of poisoning. The most familiar example of this form of tolerance is that acquired for tobacco (nicotine); the first cigar often induces violent poisoning, but if a habit be formed, considerable amounts of nicotine may be absorbed without apparent harm, not because the absorption is retarded, or the excretion is accelerated, but because the tissues become accustomed to the presence of small quantities of nicotine, and thus fail to react to it. Nicotine, in fact, becomes a normal constituent of the tissues. This tolerance is entirely different from the immunity induced by toxalbumins (see Ricin), and it is desirable that the two terms should be kept distinct. Very often while tolerance for a poison is established in certain tissues, others suffer from the prolonged use of excessive quantities; for example, although the seasoned smoker does not suffer from the nausea and vomiting which followed his first essay, other organs may in course of time become involved, such as the heart or the eye. It is to be noted that tolerance is soon lost if the drug be discontinued for some time. This is of great importance in cases of opium-eating, for a person who has taken opium for a long time acquires a tolerance for the drug, so that sometimes enormous quantities are required in order to induce the ordinary effects, but if the habit be discontinued for some time the tolerance is lost, and a dose which would formerly have had little effect may now induce dangerous poisoning. The prolonged use of one drug may establish tolerance for others of the same class. Thus chronic drunkards are not influenced by large quantities of alcohol, and are also more resistant to the action of chloroform than ordinary persons, this being due to the fact that chloroform and alcohol act on the same nerve cells in the same direction, and probably induce the same changes in the protoplasm.

The **Cumulative Effect** of drugs is another phenomenon caused by their prolonged ingestion. Small doses of certain drugs taken repeatedly for some time eventually cause symptoms which are much more marked than those caused by a single small dose. In many instances this seems due to the accumulation of considerable quantities in the tissues. The absorption may be more rapid than the excretion, and each new dose thus adds to the total quantity in the blood and organs more than is lost in the same time by excretion. The classical example of cumulative action is that of digitalis, but it is much more frequently induced by such drugs as mercury, arsenic, or the iodides, for the so-called chronic poisoning induced by these is really an example of cumulative action. It has been suggested that cumulative action is not really due to the accumulation of the drug in the tissues, but to a summation of a prolonged series of effects of the same kind; but although the increase of the drug in the organs has not been proved in all instances, it seems probable that this is the explanation in the great majority of cases, perhaps in all. Cumulative action may occur along with tolerance, as has been stated. Thus the tolerance of certain tissues for nicotine does not protect others from the effects of the abuse of tobacco.

Synergists.—The presence of another drug having the same effects in the body often increases the action of a remedy to an unexpected extent. This is the ground for the prescription of several remedies acting in the same way.[1] For example, several purgatives prescribed together often act more efficiently than any one given in quantity equal to all of them. It is quite impossible to explain this except by assuming that, although all are alike in their chief features, they differ in the details of their reactions, so that parts of the alimentary canal which might escape one are affected by another, and the mixture thus acts more universally than any one of the components. Other examples of synergism are offered by the anæsthetics, for it has been

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[1] The less important ones are sometimes termed adjuvants.

Relieve organ of work - aid nature. Can't Cure

shown that a mixture of two of these may induce anæsthesia when administered in a dilution far below that necessary if either is employed alone.

On the other hand, a drug may fail to elicit any symptoms if an **antagonistic** substance be present in the body. Thus in cases where a powerful nervous depressant, such as chloroform, has been inhaled, strychnine may have little or no effect on the spinal cord in doses which would normally increase the reflexes to a marked extent. In the same way, if the terminations of the inhibitory fibres of the heart are paralyzed by atropine, a poison which normally slows the heart by stimulating these terminations will have no such effect except in very much larger doses.

Hunt has recently discovered a series of relations between drugs, which do not seem to fall into either of these categories. Thus the administration of alcohol renders animals more susceptible to the action of acetonitrile, and thyroid feeding has the same result in rats, while it increases the resistance to acetonitrile in mice.

Similar modifications of the effects of drugs may be induced by poisons induced by pathological changes in the tissues, or by an unusual state of irritation or of depression of the tissues themselves. For example, in hot weather and in tropical climates, purgatives are found much more efficient than in colder climates, either because there is some poison which acts along with the purgative, or because the mucous membrane is more irritable than usual. That some such factor is present in these conditions is shown by the frequent occurrence of diarrhœa without the use of drugs.

Similarly when an antagonistic poison is formed in the tissues in the course of a disease, a drug may have little or no effect; so that if the inhibitory cardiac terminations are paralyzed by disease, the heart cannot be slowed by muscarine or digitalis.

Pathological conditions very often modify the effects of drugs to a very considerable extent, and in a way which cannot be explained at present. For example, the antipyretics reduce the temperature in fever, but have no effect on it in health; the bromides lessen the convulsions in epilepsy, but have much less effect in depressing the brain in normal persons. The question may therefore be raised whether the examination of the effects of drugs in normal animals is of much value in indicating their therapeutic action. But in reply it may be said that in a large number of instances drugs are given, not in order to act upon the diseased tissues, but upon healthy ones. The object of the therapeutist is very generally not to restore the diseased tissue, but to relieve it from work, and to allow it rest so as to promote its restoration by nature. For instance, in diseases of the cardiac valves, drugs are given, not with the object of restoring their integrity, but to act upon the healthy heart muscle, and to obviate the disturbance of the circulation which is caused by the destruction of the valves. In inflammation of the kidneys, the physician seldom attempts to reduce the inflammation by the action of drugs on the cells involved, but confines his attention to removing by other channels the products of tissue waste, which would normally be excreted by the kidney. So that in most instances drugs are given to act on normal tissues, or on tissues which are so little affected by disease that they react to remedies in the same way as the normal. In other cases in which the remedy acts on the cause of the disease or on the diseased tissue, its introduction is due to clinical experience only. Thus quinine destroys the organism of malarial fever, but this could never have been anticipated from its action on the normal tissues, and could only be discovered by experiments on the organism, or rather by experiments on persons suffering from the disease, as the organism has been recognized only of late years.

METHODS OF ADMINISTRATION.

The effect of a remedy is often determined very largely by the method in which it is administered. As regards the local action, this is sufficiently obvious, for an irritant applied to the skin could scarcely be expected to cause the same symptoms as if it were applied to the stomach and intestine. But the same holds true for the general action in most instances, because some tissues and organs absorb much more rapidly than others, and a larger quantity of the drug therefore passes through them into the blood in a given time. Thus, if a poison which is absorbed slowly be rapidly excreted, so little of it may exist in the blood and tissues at any given time that no effects are induced, while if it be rapidly absorbed, the same dose can exert some action before it is excreted.

Drugs are applied for their **Local Action** to the skin, to the mucous membranes of the alimentary, respiratory, and genito-urinary tracts, and to the conjunctiva and cornea. Not infrequently they are injected by means of the hypodermic needle into the subcutaneous tissues for their local effects, and the attempt is continually being renewed to treat even the deeper tissues and organs locally by the injection of remedies into them. The objects of local medication are very diverse, and can be treated of only in connection with the individual drugs. The methods of application are also so numerous that only a few of the chief can be mentioned. Drugs intended for application to the skin are often formed into salves or ointments (unguenta) by mixing them with oily or fatty substances, which adhere to the skin and do not dry up, and which in addition to serving as a means of applying an active substance, protect the surface from the air and from irritation. Other preparations for application to the skin, such as the plasters (emplastra), resemble the ointments in their general characters, but also give mechanical support and bind surfaces together from their being spread on paper or cloth, which thus serves as a flexible splint. The collodions and cerates resemble the plasters, the oleates the ointments. In addition to these special preparations, drugs may be applied to the skin in solutions, or as powders, or solid masses may be used to cauterize it.

The methods of applying drugs to the alimentary tract and to the lungs for their local action are for the most part similar to those used for drugs which are intended to be absorbed. The mouth and throat may be washed out with solutions, which are gargled (gargarismata), or may be treated with powders, or lozenges (trochisci), which are slowly dissolved and thus permit of a more prolonged and constant action in the mouth than is possible if the drug be swallowed immediately. The nose may be washed out with solutions of active drugs, or powders may be drawn into the nostrils as snuffs; the latter often cause sneezing, and are sometimes known as sternutatories, or errhines. The larynx may be treated locally by the application of powders or of very small quantities of fluids by means of the laryngoscopic mirror and probe. Solutions are generally used for application to the conjunctiva, but a more permanent effect can often be obtained from the use of ointments or powders which are less liable to be washed away by the tears. The urethra, vagina and uterus are treated by the injection of solutions, or by ointments and powders. Bougies, which are occasionally advised, are formed by incorporating an active drug in some substance which is solid at ordinary temperatures, but melts when introduced into the organ and allows the drug to come into contact with the surface. The rectum may similarly be treated by the injection of drugs in solution or suspension (enemata), or by the use of suppositories. Drugs are not infrequently applied by the rectum in order to elicit their action after absorption, but much oftener for their local action on the bowel. Enemata may be either large (a pint or more) or small (2–5 c.c., ½–1 fl. dr.). The large enemata are used either to wash out the intestines, and may then contain an antiseptic or astringent, or to induce peristalsis and evacuation of the bowel, when they are made up of water with or without soap or other slightly irritant substances. The small enemata are used chiefly to induce evacuation, and contain more irritant substances, such as glycerin alone or along with some more active body. The suppositories are formed of cacao-butter, which is solid at room temperatures, but melts at the temperature of the rectum.

All the visible mucous membranes may also be cauterized by the application of a solid rod of a corrosive for a short time.

Drugs whose **General Action** is to be elicited after their absorption are given by the mouth, except when some special character in them or in the disease renders some other method preferable. They may be given by the mouth in solution in water, alcohol, oils, or other more or less indifferent bodies. The disagreeable taste of many remedies, however, often precludes this method, and these may be ordered in the form of pills, or in capsules, which are formed of gelatin or similar substances and are dissolved in the stomach and intestines. Very often the disagreeable taste may be concealed by the addition of sugar, or of some strongly tasting but agreeable body, such as a volatile oil. Insoluble drugs may be given as powders, as they have little or no taste. Powders are also used as a means of administering soluble

(Absorption more rapid if drugs administered pure or in sol. than
dry or in comb. with other substances (inert)
G. & I. juices may dissolve insol. drugs or free sol. ones (albuminates

drugs, if they have not a disagreeable taste and have no marked local action, but very deliquescent drugs should not be given in this form. Insoluble drugs are sometimes ordered in suspension in mucilaginous fluids; and oils, which are distasteful to many people, may be given mixed with water and gums (emulsions).

The rate of absorption from the *alimentary canal* varies greatly with different drugs and also with the form in which they are administered. The first point will be treated of in connection with the individual drugs. As regards the second, it may be stated that drugs are more rapidly absorbed when they are swallowed in solution, and that when much inert and insoluble matter is associated with them, their absorption is much retarded. Thus, common salt passes more rapidly into the blood when it is dissolved before being taken than when it is swallowed dry, and morphine is absorbed much more quickly when it is administered pure than when, as in opium, it is mixed with a mass of gums and other bodies. This fact is taken advantage of in practice by giving drugs in solution when rapid absorption is desirable, and by giving less pure forms when the local action on the stomach and bowel is to be elicited. The more concentrated the solution, the greater is the irritant action on the stomach, and thus where irritation of the stomach is desired, either the solid drug or a strong solution is given; but as a general rule the local action on the stomach is to be avoided, and drugs are therefore ordered in as dilute solution as is possible without increasing the bulk to too great an extent. It is to be noted that drugs which are insoluble in the test-tube may be rendered soluble by the action of the gastric and intestinal juices, while many which are given in solution, are thrown down in the stomach in the form of insoluble albuminates.

The great mass of drugs absorbed from the stomach and intestine is carried to the liver before reaching the general circulation, and this is of great importance in determining their effects in the body, as some of them are retained in that organ, and are either entirely destroyed or escape so slowly that they have no perceptible effect.

Another important method of administering drugs for their general action and also for their local effects is by inhalation into *the lungs.* Only volatile drugs can be used thus for their general action. They are absorbed very rapidly owing to the extensive surface to which they are applied, and also because volatile substances penetrate the tissues more readily than others. The best examples of inhalation are offered by the general anæsthetics, chloroform and ether. Most substances absorbed by the lungs are also excreted by them, and this leads to an important practical point in regard to the anæsthetics. For the passage of gases or vapors through the lining epithelium of the alveoli depends in most instances[1] upon their partial pressure, that is, upon their concentration in the air and blood respectively. Accordingly, when the air contains more chloroform vapor than the blood, the anæsthetic passes

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[1] **Such gases as oxygen and carbon monoxide, which form chemical combinations with the hæmoglobin, are of course exceptions.**

Non vol drugs in water not [illegible] by skin, Alkaloids even in fats & Alcohol not resorbed. Hg via skin to avoid local effects on bowel
nonirritant Drug not prec at point of injection & sol. Hg be injected by hypo
In water, oil or dil alcohol.

into the blood, but as soon as the condition is reversed, and the blood contains more chloroform than the air of the alveoli, it commences to pass backwards. The more concentrated the vapor inhaled, the more chloroform is contained in the cubic centimeter of blood, and the greater is the action on the nervous centres and the heart.

Less volatile substances are sometimes inhaled into the lungs for their local action, and even non-volatile bodies suspended in a spray of vapor may be thrown into the respiratory passages, but it may be questioned whether these last really reach the alveoli except in traces.

Drugs are also applied to *the skin* in order to elicit their general action. Volatile bodies are certainly absorbed by it, although much more slowly than by the lungs or by the stomach and intestine. Solutions in water of non-volatile drugs are not absorbed from the skin, but solutions of certain remedies in alcohol, oils, fats, ether, and some other substances which are capable of dissolving or mixing with the fatty covering of the skin, are absorbed fairly rapidly if they are rubbed in thoroughly. This method of application (inunction) has been used chiefly for the absorption of mercury, as the local action on the stomach and bowel is thus avoided. (See Mercury.) Alkaloids do not appear to be absorbed by the skin even when dissolved in oils or alcohol. An entirely obsolete method of application is the endermic, in which the epidermis was removed by a blister, and the remedy then applied to the exposed corium.

The *hypodermic method* is of comparatively recent origin, but is being more widely used every year. In it drugs are injected through a fine hollow needle into the subcutaneous, or, in the case of more irritant substances, into the muscular tissue, where they meet with fewer sensory nerves. Absorption occurs more rapidly than when drugs are given by the mouth, the local action on the alimentary canal is avoided, and the physician is more certain that the whole of the remedy is effective, provided it is soluble and is not precipitated at the point of injection. At the same time, the method has certain drawbacks, the chief of which are the pain of the injection and the danger of injecting a powerful remedy into one of the subcutaneous veins. Hypodermic injection should be made only by the physician or trained attendant, for incalculable injury has been done by entrusting patients with the syringe, particularly for the injection of morphine and cocaine. The needle and syringe ought to be disinfected, and the substance injected should be aseptic, and this renders the method inconvenient. As a general rule, solutions in water or in dilute alcohol are used for injection, but the insoluble salts of mercury have also been injected, suspended in oil (see Mercury). Irritant drugs are to be avoided as far as possible, as they cause great pain, swelling and sometimes suppuration, even when the injection has been carried out aseptically. Hypodermic injection is used very largely to elicit the general action of a remedy, but also for the local effects, as when cocaine is injected in order to produce local anæsthesia. Solutions of inert bodies have also some anæsthetic

Subcutaneously hypo = rapid absorption, so reduce dose 1/2
Intravenously = " "
By rectum

action, probably owing to their mechanical action on the sensory nerve fibres. As the absorption from the subcutaneous tissues is so much more rapid than that from the stomach and intestine, when the drug is in perfect solution the dose has to be reduced. As a general rule, about one-half of the ordinary amount is sufficient.

Deeper injections are sometimes made for their local action on the organs. Thus, antiseptics have been injected into lung cavities, caustics have been injected into tumors, and direct applications have been made to the nerves in sciatica and other similar disorders.

Intravenous injection is the most certain method of bringing drugs into the circulation and tissues, and is at the same time the most rapid. It is, therefore, very largely used in experiments on animals, but has generally been considered too dangerous for therapeutic purposes in man. Baccelli has, however, recommended it highly in recent years in cases of emergency, in which the immediate action of a remedy is required. In pernicious malaria, and in syphilis when an important organ is threatened, he has injected small quantities of quinine and mercury with great success. Cardiac and circulatory stimulants, such as digitalis and adrenaline, have also been administered in this way. The dose must be very much smaller than that employed by the mouth, but it is impossible as yet to state exactly what fraction will induce the same effects.

Drugs are occasionally applied by *the rectum* for their general action, as has been mentioned. The local effects on the stomach are avoided by this method, and morphine and opium are, therefore, not infrequently administered thus. The rate of absorption from the rectum as compared with that from the stomach and bowel is still a disputed point, and some physicians recommend that the dose be reduced to three-fourths, while others recommend one and one-half times that given by the mouth.

Drugs are not administered by the *other mucous membranes* for their general effects, but it must not be forgotten that symptoms may arise from their application to them for their local action. Similarly, drugs applied as dressings to *wounds or abrasions* have very often given rise to severe or fatal poisoning from being absorbed into the blood and tissues.

THE CHEMICAL CHARACTERS OF DRUGS.

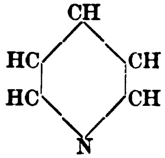
An enormous number of substances induce changes in the living organism, and have, therefore, to be recognized in pharmacological treatises. Many of them are comparatively simple chemical compounds, and require no general description here, but less attention is paid in ordinary chemical text-books to certain groups of active poisons, and some note must be taken of their general properties.

In the inorganic materia medica are found many salts, bases and acids, and a few uncombined elements, such as mercury and phosphorus.

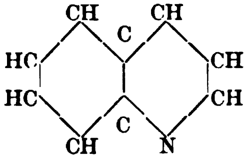
Inorganic & organic comp.
Alkaloids = substituted ammonias - alk. = "vegetable bases". Comb with acids
without eliminating H - Thrown out of comb by fixed ~~[illegible]~~ alk.
Pyridine (iso) quinoline derivatives

Organic chemistry offers a large and ever-increasing number of artificial compounds which belong to almost every one of the divisions recognized in chemistry. The hydrocarbons, alcohols, ethers, phenols, ketones, aldehydes, acids, and many others, contribute active agents, and in fact most of them are represented by one or more members in therapeutics. They may all be regarded as sufficiently known by students who are prepared to study pharmacology with profit, but some substances, obtained chiefly from plants, require further mention.

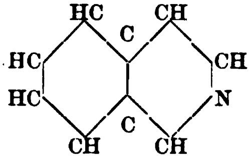
The first group of these is formed by the **Alkaloids**, which are substituted ammonias, and have a more or less strongly alkaline reaction, so that they are often known as the vegetable bases. They contain carbon, hydrogen, nitrogen, and, as a general rule, oxygen, although some of them, such as coniine, are devoid of it. Like ammonia, they combine with acids readily without eliminating hydrogen, and the salts thus formed resemble those of ammonia in many respects, among others in being thrown out of combination by the fixed alkalies. The term alkaloid is often restricted to compounds of pyridine and quinoline, but this narrow definition cannot be maintained in treating them from the pharmacological point of view. It is true that most of the vegetable alkaloids whose constitution is known are derived from pyridine, quinoline and isoquinoline by the addition of hydrogen, and generally by the substitution of one or more of the hydrogen atoms by side chains of greater or less complexity.



Pyridine.

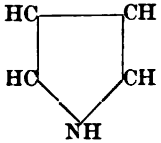


Quinoline.

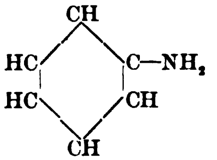


Isoquinoline.

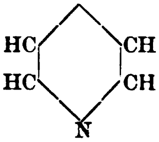
But others appear to be derivatives of the pyrrol and oxazine groups, while in others the nitrogen is attached to radicles belonging to the methane or open-chain series, as in $CH(OH)_2—CH_2—N(CH_3)_3OH$, which is generally regarded as the formula of muscarine. Another series of bodies, which may be regarded as alkaloids, although they differ from the others in many respects, are derivatives of aniline, and are artificial products.



Pyrrol.



Aniline.



Oxazine.

These aniline derivatives bear some relation to the vegetable bases in their action, but are equally or more nearly related to the benzol series, so that they may be regarded as connecting links between these two classes of bodies. Finally the purine bodies (see Caffeine group)

Prec by tannic acid by KI + I by hydrates + carbonates of the alkalis

may be mentioned in this connection, although their chemical structure scarcely permits of their being numbered among the true alkaloids.

Some of the vegetable alkaloids have been formed synthetically in the laboratory, and the constitution of some of the others is perfectly well known, but many of them have not yet been isolated, and there are probably others whose existence is not even suspected. These vegetable alkaloids occur in almost all parts of plants, although they are found in greatest abundance in the seeds and roots. The same alkaloid is often found in most of the plants of a genus, or it may occur in one or two species of a genus and in other plants which are in no way related. Very often more than one alkaloid is found in a plant, and these may differ entirely in their action on animals, although not infrequently all the alkaloids of a plant resemble each other in their effects. The alkaloids are found almost exclusively in dicotyledonous plants, only one or two being known to exist in the monocotyledons. Muscarine, ergotoxine and other bases are found in the fungi, and quite recently alkaloids have been isolated from the suprarenal capsule of animals and from the skin of the salamander.

The alkaloids are very often only slightly soluble in water, but form salts which are generally more soluble. Many of the bases are dissolved in ether, chloroform and amyl alcohol, while the salts are insoluble in these. Both bases and salts are generally fairly soluble in alcohol. The alkaloids are precipitated from solution by a large number of reagents, of which the most important are the chlorides of platinum and of gold, tannic acid, phosphotungstic and phosphomolybdic acid, the double iodides of potassium and mercury, and of potassium and cadmium, and iodine held in solution in water by potassic iodide. The hydrates and carbonates of the alkalies and the alkaline earths precipitate the alkaloids from solutions of the salts in water, a point of some importance in prescribing these bodies. In cases of poisoning when the alkaloid has been taken by the mouth, it may be precipitated in the stomach by dilute alkalies or better by tannin solutions. The poison should then be removed by inducing vomiting or by washing out the stomach with the stomach tube.

Another important class of vegetable poisons is formed by the **Glucosides** (glycosides), or saccharides, which are esters (compound ethers) composed of sugars and hydroxyl substances, and which liberate sugar when they are heated with acids, or sometimes with alkalies, or when certain unorganized ferments act on them. The sugar formed in this way is often glucose, but not invariably so; the other decomposition products have been identified only in a few instances. Many of the glucosides contain only carbon, hydrogen and oxygen, a few have nitrogen in addition and one or two sulphur. In some instances the remainder, after the sugar is split off, is an alkaloid, *e. g.*, solanidine. Glucosides differ greatly in their solubility in water and alcohol; comparatively few of them are soluble in ether. Some of the glucosides are powerful poisons, others have little or no action.

Resins, an ill-defined group, are found in many plants, and are char-

Resins insol in H_2O. Sol in alcohol, ~~etc~~ ether, Vol. oils
Oleoresin
Balsam = 1 + benzoic acid
Vol. oils. Neutral principles

Gum resin - insol in H_2O, but resin suspended by gum. Or resin → alcohol, gum insol

acterized by their smooth, shining fracture, and by their insolubility in water and solubility in ether, chloroform, volatile oils, benzol and, in many cases, in alcohol. They seem to be formed in plants by the oxidation of volatile oils, and are often acid or anhydride in character, while others are apparently alcohols or esters. The resins are almost invariably composed of several different substances mixed together. Many of the resins are local irritants, and some are poisonous in comparatively small quantity from the powerful action they exert on the intestine.

Oleoresins are solutions of resins in ethereal oils, which lend them a characteristic odor and taste.

The term '*Balsam*' is often used as synonymous with oleoresin, but most writers restrict it to those oleoresins which contain benzoic and cinnamic acid along with other constituents. (See Benzoic Acid.)

Gum-resins are mixtures of resins and gums, generally containing some volatile oils. They are insoluble in water, but the resin is suspended in it by the gum. On the other hand, the resin is dissolved by alcohol, while the gum remains insoluble.

Gums are amorphous, transparent substances, composed of carbohydrates of the formula $C_6H_{10}O_5$ and are thus nearly related to cellulose and starch. Some of them are soluble in water, while others merely swell to a jelly in it; they are insoluble in alcohol. They generally occur in plants in combination with calcium, magnesium or potassium; they have no poisonous action, but form a protective covering for irritated surfaces, and are largely used to suspend in water substances which are insoluble in it, such as resins and oils.

Volatile oils occur in plants in large numbers. (See page 58.)

Many Acids which are of pharmacological and therapeutic interest are obtained from plants, but it is unnecessary to enter into a description of their properties here.

Fats and oils, sugars, starch, proteins, coloring matter, ferments and other bodies which occur in plants, and are contained in many of the preparations used in therapeutics, are not generally possessed of any action of importance. Those which are active in the body will be described individually.

Neutral Principles

Finally many of the active principles of plants are entirely unknown or have been only partially examined. Among these are a number of substances which have little in common except their bitter taste and which are known as **Bitters**.

THE PHARMACOPŒIAS AND PHARMACOPŒIAL PREPARATIONS.

Almost all governments have found it necessary to regulate the preparation of drugs used in therapeutics, and for this purpose issue at intervals codes of instructions defining the characters of the drugs and giving the exact formulæ according to which they are to be prepared for use. In the United States, where the government has not undertaken this as yet, a code has been prepared by a voluntary association of physicians and pharmacists. These codes are known as **Pharmacopœias**, and some differences exist between those of different states, although the most important drugs are found in all of them. All the drugs used in therapeutics are not found in the pharmacopœias, for these are issued only at intervals of several years, and in the meantime large numbers of remedies are introduced, used for a few months, and pass into oblivion. Even when a drug maintains its position for many years, and promises to be a lasting addition to therapeutics, it often fails to be admitted to the official code, while others of older standing, which are comparatively seldom used, and which might be omitted without loss, are kept on the list. This conservative tendency of the compilers of the pharmacopœias has its disadvantages, but at any rate tends to withhold official sanction from the innumerable ephemeral products of chemical industry. The official definition of therapeutic substances is of advantage to both physician and pharmacist, as it assures the former that the drug he prescribes will have a uniform quality, wherever in the country it is dispensed, while the pharmacist is saved from the continual preparation of remedies in different forms, by their being prescribed in one recognized strength.

The pharmacopœias contain a large number of pure substances such as salts, acids, bases, alkaloids, and these require no further description. On the other hand, many of the drugs are given in an impure form, either because the active principle is unknown, or because its isolation is attended with difficulty and expense. Thus many of the vegetable remedies are presented in the pharmacopœias as solutions or solids which contain not only the active principle but gums, sugars, coloring matter, and many other impurities. These are provided in different forms to allow of variation in their administration. In addition, the pharmacopœias contain a number of official prescriptions, that is, mixtures of active substances in such proportions as are ordinarily prescribed. These are generally designated by the addition of compound (compositus) to the name of the chief ingredient. Most pharmacopœias continue to use Latin in the titles of the drugs, and this is not due to mere pedantry or conservatism, as is often stated. For the popular name of a drug is often used for several different substances, as, for example, hellebore, while the Latin name in a prescription indicates that drug which is known by the term in the pharmacopœia. In the same way it is found necessary to maintain Latin terms in botany and zoology in order to define accurately the species.

Many crude or unprepared drugs are found in the pharmacopœias, such as leaves, roots, flowers, or even whole plants. These are used chiefly for the preparation of other more readily applicable remedies, but are sometimes prescribed as powders or in pills.

The following preparations[1] are official:

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[1] The student is advised to omit the following list for the present, and to refer to it only as he takes up the preparations of the individual drugs. Most of these preparations are found in both pharmacopœias. Those which occur only in the British are indicated by B. P., while those which are confined to the United States are marked U. S. P.

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a. *Aqueous Preparations.*

Vol. sub. in H_2O

Aquæ, medicated waters, generally contain only traces of some volatile substance, such as an ethereal oil or chloroform, in solution in water, and these are used in prescriptions as more agreeable to the taste and smell than pure water but have no further effect. In the U. S. P. the solutions of chlorine, ammonia and hydrogen peroxide are also included under aquæ, but these are used only to elicit the specific effects of these drugs and are powerful poisons. In the B. P. these strong solutions are included in the liquores.

Non vol in H_2O

Liquores (U. S. P.) are solutions in water of soluble substances which are not volatile. The official solutions of powerful poisons are often one per cent. in strength.

Liquores (B. P.) are solutions in the widest sense, in water, alcohol, or other fluids. The dissolved substance may be volatile or non-volatile. The "concentrated solutions" (B. P., *Liquores Concentrati*) are not, as might be supposed, condensed by evaporation. They resemble infusions and decoctions in most respects.

[illegible] drug + boil H_2O

Decocta, or decoctions, are impure solutions of vegetable principles, which are obtained by boiling parts of plants in water.

[illegible] infuse [illegible] in water

Infusa, or infusions, are solutions obtained by soaking parts of plants in water, which may be hot or cold, but is not kept boiling. Infusions and decoctions are weak preparations and decompose rapidly so that they are used only when recently prepared.

[illegible] the [illegible] in H_2O [illegible] bodies

Misturæ (U. S. P.), or mixtures, are preparations in which substances insoluble in water are suspended in it by means of gums or similar viscid substances.

Misturæ (B. P.) include a number of preparations in which insoluble bodies are suspended in water by means of gums or syrup, but one mixture contains only soluble bodies.

[illegible] suspended in H_2O oil = emulsions

Emulsa (U. S. P.), emulsions, are formed by suspending oils in water by means of gums or other viscid bodies. The B. P. contains no official emulsions, the corresponding preparations being known as *misturæ*.

Mucilagines, mucilages, are solutions in water of gums, starch, and similar bodies.

Strong sol of sugar in H_2O

Syrupi, syrups, are strong solutions of sugar in water, which may be used alone, or may be impregnated with more active bodies. Similar preparations formed with honey instead of syrup (sometimes known as *mellita*) are official, as Mel Rosæ (U. S. P.), Mel Boracis (B. P.). A solution of honey and acetic acid is known as *oxymel* in the B. P. (Oxymel Scillæ).

Hg.

Lotiones (B. P.), lotions, or washes. This term is used to designate two preparations of mercury, the black and yellow wash.

b. *Alcoholic Preparations.*

It is to be noted that in these preparations the menstruum (alcohol) is not an indifferent body as in the aqueous preparations; the effects of some of this class are undoubtedly due rather to the alcohol than to the dissolved substances.

Vol. sub in alcohol

Spiritus, spirits, are solutions of volatile bodies in alcohol, and often owe their chief action to the solvent and not to the drug contained in it.

Ditto + sugar

Elixiria (U. S. P.), elixirs, differ from spirits chiefly in containing sugars, which are added in order to give them taste.

Vol & non-vol substances in alcohol by soaking plant.

Tincturæ, tinctures, are solutions in alcohol of medicinal substances, which are generally formed by soaking parts of plants in it. They contain both volatile and non-volatile ingredients, but the latter are generally the more important.

Fluidextracta (U. S. P.), *Extracta Liquida* (B. P.), fluid extracts, are prepared from plants by forming solutions in water or more frequently in

✓

alcohol, and evaporating them until the solutions contain as many cubic centimeters as the original crude drugs weighed in grammes; that is the volume of the fluid extract corresponds to the weight of the crude drug.

Fluids ext. n alcohol. As many cc as plant wt in grams

The tinctures and fluid extracts are the most commonly used liquid preparations, and most of the important drugs are prepared in one or both of these forms.

Vina, medicated wines, are solutions of active substances in wine or in dilute alcohol.

medicated wines

Succi (B. P.), the juices of fresh green plants, obtained by pressure. Some alcohol is added to preserve them from putrefaction.

c. *Other Fluid Preparations.*

Glycerita (U. S. P.) or *Glycerina* (B. P.) are solutions of medicinal substances in glycerin.

medicine in glycerine

Collodia, collodions, are solutions of medicinal substances in collodion. (See Part VI.)

Aceta, or medicated vinegars, are solutions of medicinal substances in vinegar or acetic acid.

Linimenta, liniments, embrocations, are preparations in which active remedies are dissolved or suspended in dilute alcohol, oils, or water. They generally contain an oil or soap and are intended to be applied to the skin.

medicines in alcohol, oil n water

d. *Solid and Semi-Solid Preparations.*

Extracta, extracts, are formed from solutions such as tinctures, decoctions, or infusions by evaporation, which is continued until there remains a solid mass. The extracts thus contain all the substances which are taken up by the solvent, except those which are driven off or decomposed by the temperature at which evaporation is carried on.

Pilulæ, pills, are globular masses of small size, such as admits of their being easily swallowed. They are formed from extracts, or from powders, by the addition of some substance to give them the necessary cohesion and consistency. Pills generally weigh 0.1–0.3 G. (2–5 grs.). The U. S. P. determines the composition and size of the official pills, so that the dose can be modified only by ordering several pills to be taken at one time. The B. P. leaves the pills unformed, so that they may be prescribed of any size. The Pilulæ of the B. P. really correspond not to the Pilulæ, but to the Massæ of the U. S. P.

Pill weigh
2-5 grs

Massæ (U. S. P.), masses, are preparations made up of the proper consistency for pills. They are invariably prescribed in the form of pills.

Confectiones, confections or electuaries, are soft, solid preparations consisting of sugar or honey impregnated with some more active body.

medicine in sugar or honey

Suppositoria, or suppositories, are intended for insertion into the rectum, urethra, or vagina, and are, except in one or two cases, formed by mixing the active ingredient with cacao-butter. (See Part VI.) Suppositories for the rectum are conical in shape and weigh about a gramme (15 grs.). Those for the urethra are of the same weight, but are pencil-shaped, while the vaginal suppositories are globular, and weigh about 3 grammes (45 grs.).

Cacao-butt

Pulveres, powders, are simply dry substances in a state of fine division. Most of the official powders are mixtures of several active bodies.

Triturationes (U. S. P.), triturations, are formed from powders by diluting them with nine parts of sugar of milk.

Powder + 9 pts milk sugar

Trochisci, troches, or lozenges, are solid masses, generally of a flattened shape, and consist of powders or other bodies, incorporated in sugar and gum. A very friable form of lozenge known as *Tabellæ,* or tablet triturates (not official), is formed by pressing in moulds a mixture of powdered sugar and drugs, slightly moistened with alcohol.

Powder + sugar + gum

sugar + medic. + alcohol

✓

Lamellæ (B. P.), or discs, are small discs formed of gelatin with some glycerin, each weighing $\frac{1}{60}$–$\frac{1}{30}$ gr. They are impregnated with an active drug, and are applied to the conjunctiva in order to elicit the local effects.

Unguenta, ointments, salves, are soft, oily substances which are applied to the skin by rubbing. (See page 48.)

Oleata, solutions in oleic acid resembling the ointments in appearance and uses.

Cerata (U. S. P.), cerates, resemble ointments, but are rendered harder by the addition of wax. (See page 51.)

Emplastra, plasters, are adhesive bodies of a still harder consistency than cerates, and soften only when heated. (See Part VI.)

Chartæ, papers, are preparations of active substances which are spread in a thin layer upon paper, or are incorporated in it by dipping sheets of paper into a solution.

UNOFFICIAL PREPARATIONS.

Cachets, are thin discs of dough of the shape of a soup-plate and varying from ½ in. to 1½ in. in diameter. When two of them are placed together with their concave sides toward each other, they form a receptacle in which powders are dispensed. The edges stick together when they are moistened. A somewhat similar method of dispensing is in gelatin *capsules,* which may be hard or soft, and which are made in different sizes. The hard capsule is used for solids, the soft for liquids. Sometimes the latter contain as much as 15 c.c. (½ fl. oz.), but these are difficult to swallow.

Cataplasmata, or poultices, are not official preparations now, but are in common use. They are generally made of linseed meal, oatmeal, or bread crumb, which is formed into a paste with hot water, enclosed in thin cotton or linen and applied to the skin. Mustard and other remedies may be added to the poultice in order to induce special effects, and in some cases a poultice consists merely of drugs enclosed in a cloth sack, as in charcoal or spice poultices.

Poultices
oatmeal, bread
crumb + seed
(as mustard)
in cloth +
hot water

Enemata, clysmata, or clysters, are liquid substances injected into the rectum for their local or general effects. (See page 32.)

CLASSIFICATION OF DRUGS.

Writers on pharmacology and therapeutics arrange drugs on many different principles. Thus a somewhat antiquated system classifies the vegetable remedies according to the botanical families from which they are obtained, but there is little advantage in this arrangement, for an order may include drugs which differ entirely in their action and in the therapeutic uses to which they are put, while, on the other hand, two widely separated botanical groups may contain identical poisons. Another classification of drugs is according to their therapeutic effects, and this might seem at first sight the most convenient for students of medicine. This plan has its drawbacks, however, for many drugs are used for a large number of different purposes, and it is impossible to describe them under each heading. In addition, the classification in groups is always liable to suggest a much closer resemblance in the effects of the individual drugs than really exists. Thus the drugs often classed as "cardiac stimulants" differ much, not only in their effects on the body in general, but in their action on the heart, and opinions may differ as to whether some of them stimulate or depress the heart. They certainly cannot be substituted for each other in the treatment of heart disease, as is suggested by their being classified together under this heading. Finally, practical therapeutics can be taught only in the clinic, and in the teaching of pharmacology it seems advisable to direct the student's attention rather to the action of drugs than to the practical uses, which can be taught to much greater advantage in connection with the symptoms, prognosis, and other clinical features of disease. The classification of drugs and poisons according to their action on living matter is the natural one, and is based on the same logical principle as the modern classification of plants in botany and of animals in zoology. The object is to group together those substances which have most points of resemblance, whether they are obtained from the same or from different orders of plants, and whatever relation they may bear to each other in therapeutics. This classification, which was introduced by Buchheim, has been further developed by Schmiedeberg and his pupils. In the present state of knowledge it is necessarily imperfect, and many resemblances and affinities have not gained that recognition which they will doubtless receive in the future. Even in its present imperfect form, however, this classification is the most satisfactory one available, and, unlike the others, it can be easily subjected to such modifications as the advance of science renders necessary.

Resemblance in pharmacological action does not necessarily involve similarity in chemical composition, as has been already pointed out. But it is found that in many instances the members of a pharmacological group have some general chemical character which distinguishes them from others.

In this volume, the classification adopted is that of Buchheim and Schmiedeberg, with some slight alterations which seemed to be demanded by recent progress. The drugs are thrown into a large number of groups which are named from the most prominent member, or from some marked property possessed by all. These groups are arranged, as far as possible, according to their mutual resemblances. It has been found advisable to retain, for the most part, the divisions into organic and inorganic drugs, although this may, perhaps, have to be abandoned in the future. The first series of groups of the organic materia medica are possessed of the common property of inducing more marked local than general effects, and these may therefore be classified in one large subdivision. The second division of the organic drugs is formed of those whose pronounced general action obscures their local effects, when these are not entirely absent. The first few groups of this division are formed of those whose chief action is developed on the central nervous system; then follow those which involve more especially the peripheral organs; these, again, pass into a series in which local irritant action is associated with powerful general effects, and through these into a series of protoplasm poisons. The groups of the inorganic drugs show less defined affinities, and are much more difficult to classify than the organic series. The salts of the alkalies and alkaline earths, the acids and alkalies may be thrown into a large and somewhat heterogeneous division, which is easily marked off from that of the heavy metals, which have many points in common in their effects in the organism, as in their chemical reactions. The latter division is led up to by phosphorus and arsenic. Another class is formed of a number of substances which are either present in the normal body, or are merely substitutes for normal secretions, and the final class is composed of a few preparations which are used only for their mechanical effects, and which for the most part are not drugs, although they are included in the pharmacopœias.

It must be emphasized that no attempt is made to draw hard and fast lines of demarcation between the different groups. The essential features of the natural system involve the recognition that this is impossible. It has therefore been considered best not to indicate any definite point at which the discussion of poisons acting on the central nervous system ends and that of the drugs with peripheral effects begins. The student is always liable to lay more importance on such divisions than is intended by the writer, to list those on one side of the dividing line as central, those on the other as peripheral in action, whereas the transition is gradual. The six chief divisions are therefore the only ones indicated.

Demulcents - adhere to mem. & protect. - Gums, sugars, Starches.

PART I.

ORGANIC SUBSTANCES WHICH ARE CHARACTERIZED CHIEFLY BY THEIR LOCAL ACTION.

This class contains a very considerable part of the drugs included in the pharmacopœias, although it bears a smaller proportion than formerly to the other classes. There is still, however, in it a large number of drugs which have practically identical effects, and there is no question that it might be considerably curtailed without loss to therapeutic practice. Many of its members are irritants, and these have been subdivided for convenience into groups according to the organs on which they exert their chief action and the purposes for which they are used in therapeutics, as gastric, intestinal, cutaneous irritants. Others act as protectives, covering injured surfaces (demulcents, emollients), and still others precipitate the proteids on the surfaces to which they are applied (astringents). Others seem to act chiefly by affecting the taste, and finally a group which is used in the treatment of intestinal parasites, has been inserted here.

I. DEMULCENTS.

A large number of colloid substances—chiefly gums, dextrins, sugars and starches—owe their use in medicine, not to any changes they produce in the cells with which they come in contact, but to the fact that they are cohesive and serve to protect surfaces mechanically. When they are applied to a sensitive surface, they retard the movement of fluid or air against it and thus preserve it from the effects of these agents. This may be illustrated by familiar examples in which the taste of food is altered by their presence, although they have often no taste or odor in themselves. Sugar dissolved in mucilage tastes less sweet than in water, and acids are also less appreciated, as may be observed in many fruits. For example, the raspberry contains more acid and less sugar than the currant, but in the former the acid taste is concealed by the presence of large quantities of colloids, so that the raspberry is regarded as a sweet fruit, the currant as an acid one. Even cold is felt less when a colloid substance is present in the fluid swallowed; thus, ice-cream or iced milk does not feel so cold on the tongue and throat as frozen water, because the colloid proteid substances form a protecting layer over the surface, and prevent the cold mass from reaching the sensory terminations so freely as it otherwise would. A number of experiments carried out by Tappeiner[1] show that other

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[1] *Tappeiner,* Archives internat. d. Pharmacodyn., x., p. 67.

ition with substances may lessen pain from irritation. Prevent
id action, + modify action. Prevents rapid resorption. Are colloids
slow resorption = fermentation + bact = irritation. Olive oil to g.i.

organs may be protected in the same way by colloid solutions. Strong salt solution applied to a motor nerve first stimulates and then slowly paralyzes it, but Tappeiner found that both of these effects are much less marked if the solution be made up with mucilage instead of with water, because the salt does not reach the nerve so readily. In the same way, intense pain is caused in a wound by strong salt solution, but is much less severe if the solution contain colloid material.

When demulcents reach the stomach, they appear to coat the wall and thus to alter the sensation arising from food, for Quincke found in a case of gastric fistula that the patient could distinguish milk from water even when it was passed directly into the stomach, and Pawlow states that the presence of starch in the stomach alters the secretion induced by food. Tappeiner found that much less inflammation of the intestine is caused by irritants if they are suspended in demulcents than if they are dissolved in water; at the same time the presence of colloid unabsorbable bodies may increase the efficiency of purgatives by preventing their absorption in the upper part of the bowel. The digestion of proteins outside the body is retarded by the presence of the demulcents, and probably this is also true of the process in the stomach. Colloid bodies also retard the absorption of fluids from the stomach and bowel, and this leads to a feeling of distention, which is much less marked if the same amount of fluid be swallowed without colloid; for instance, water is absorbed more rapidly than milk or beer.

The slow absorption of colloid fluids allows time for decomposition, and this may give rise to irritation and catarrh. The colloids themselves are absorbed very slowly, and probably only in a condition of semi-decomposition. After absorption, they are oxidized in the tissues and therefore act as foods to some extent, although their slow absorption prevents their being of much value. They have, of course, no effect as demulcents after absorption, but the large quantity of fluid with which they are generally taken may be of benefit in some conditions.

Demulcents **are used** to cover inflamed surfaces; in tonsillitis, for example, they may be applied as gargles, or better by sucking lozenges containing them. They are not often applied externally for this purpose, as they are liable to serve as media for the growth of micro-organisms. In gastric and intestinal catarrh their use is objectionable for the same reason, their slow absorption leading to decomposition with the formation of irritants, which may do more harm than is counterbalanced by their protective action. Instead of demulcents, some of the oils, such as olive oil (p. 50), have been recommended as protectives in disease of the stomach and intestine.

In acute irritant poisoning the demulcents are often of great value, as they protect the stomach wall from the effects of the poison. The best remedy in these cases, because the most readily obtainable, is milk or white of eggs.

Their effects in retarding the absorption of other remedies may be

Starch gel in enemata for resorption as irritation (+ peristalsis) warded off

taken advantage of. Thus when the effect of alcohol on the stomach or bowel is desired, it is given as wine, which contains colloid material, and is therefore absorbed slowly; it must be noted, however, that these same colloids delay digestion much more than alcohol itself. In the same way opium and extract of nux vomica are prescribed when the local action on the bowel and stomach is desired, while the pure alkaloids, morphine and strychnine are administered for their effects after absorption.

Demulcents are often given instead of pure water in cases where it is desired to administer large quantities of fluid, as they have more "body" and are more agreeable to the taste. Thus, barley water or some other demulcent may be advised in order to assuage the thirst of fever, or to dilute the urine when it is too concentrated or too acid.

Demulcents are often used as the basis of enemata which are intended to be absorbed, because solutions containing colloids are less irritant and therefore less liable to set up peristalsis than pure water. For this purpose starch solution is generally used.

Some of the gums, notably acacia and tragacanth, are seldom advised as demulcents, but are often prescribed in order to hold in suspension in water such insoluble bodies as resins and oils, or to give cohesion to pills and lozenges.

PREPARATIONS.

Acacia (U. S. P.), **Acaciæ Gummi** (B. P.) (gum arabic), a gummy exudation obtained from Acacia Senegal, consists of the potassium, magnesium, and calcium salts of a weakly acid substance, arabin or arabinic acid ($C_6H_{10}O_5$). It is soluble in equal parts of water, and is used as a demulcent, but more largely as a vehicle for other drugs.

MUCILAGO ACACIÆ (U. S. P., B. P.).—About 1 part acacia in 2 of water. Dose, 16 c.c. (4 fl. drs.). 34% 16cc

Syrupus Acaciæ (U. S. P.). 10%

Tragacantha (U. S. P., B. P.), a gummy exudation from various species of Astragalus, contains salts of arabin and tragacanthin. Tragacanthin differs from arabin in not dissolving, but merely swelling up into a jelly in water. Tragacanth is used chiefly to suspend heavy powders in water.

MUCILAGO TRAGACANTHÆ (U. S. P., B. P.), formed of tragacanth, glycerin and water. In the B. P. alcohol is used instead of glycerin. Dose, 16 c.c. (4 fl. drs.). 16 cc

Glycerinum Tragacanthæ (B. P.), a solution of tragacanth in glycerin and water.

Pulvis Tragacanthæ Compositus (B. P.), contains tragacanth, gum acacia, starch and sugar. Dose, 20–60 grs.

Amylum (U. S. P., B. P.), or starch, may be formed into a jelly by boiling in water, and may then be used for the same purpose as the demulcents.

Glyceritum Amyli (U. S. P.), *Glycerinum Amyli* (B. P.), is a jelly formed by heating starch with water and glycerin.

Amygdala Dulcis (U. S. P., B. P.), or sweet almonds, the seed of Prunus amygdala dulcis, contains a fixed oil and emulsin, a ferment, but, unlike the bitter almond, no amygdalin. When triturated with water it forms an emulsion, or mixture, which is bland and demulcent.

Emulsum Amygdalæ (U. S. P.). Dose, 120 c.c. (4 fl. oz.).

Pulvis Amygdalæ Compositus (B. P.), contains sugar and acacia with almond.

✓ *Syrupus Amygdalæ* (U. S. P.) is formed from a mixture of sweet and bitter almonds, and therefore contains a small proportion of prussic acid, but may be used in the same way as the demulcents with perfect safety.

✓ **Glycyrrhiza** (U. S. P.), **Glycyrrhizæ Radix** (B. P.), or liquorice-root, the root of Glycyrrhiza glabra (var. glandulifera), is used as a demulcent, and sweet more largely to flavor medicines. It has a pleasant, sweet taste, owing to the presence of *Glycyrrhizin*, an acid glucoside, which is combined with jelly in H_2O calcium and ammonia in the plant, and is not soluble in cold water, but swells up in it to a jelly-like mass. Glycyrrhizin is probably decomposed in the body; the urine is often found to contain a reducing body after the administration of liquorice.

EXTRACTUM GLYCYRRHIZÆ (U. S. P., B. P.). Dose, 1 G. (15 grs.).

1 G. *Extractum Glycyrrhizæ Purum* (U. S. P.). Dose, 1 G. (15 grs.).

Fluidextractum Glycyrrhizæ (U. S. P.), *Extractum Glycyrrhizæ Liquidum* 2 c.c. (B. P.). Dose, 2 c.c. (30 mins.).

Glycyrrhizinum Ammoniatum (U. S. P.), the ammonium salt of glycyrrhizin.

PULVIS GLYCYRRHIZÆ COMPOSITUS (U. S. P., B. P.), contains senna. Dose, 2-8 G 2–8 G. (30–120 grs.).

TROCHISCI GLYCYRRHIZÆ ET OPII (U. S. P.).

Brown Mixture 15-30 cc ✓ MISTURA GLYCYRRHIZÆ COMPOSITA (U. S. P.), "*Brown Mixture*," contains opium, antimony and spirits of nitrous ether. Dose, 15–30 c.c. (1–2 tablespoonfuls).

The extract is largely used in the form of lozenges for its demulcent action, and is very frequently used to make up pills. It is slightly laxative, and may be used as a pleasant aperient for children; the compound powder is more reliable for this purpose owing to its containing senna, one of the vegetable purgatives.

The lozenges and the brown mixture contain opium and are used largely in cough and in catarrh of the air passages.

Numbers of other substances are used as demulcents in domestic medicine, and are found in different pharmacopœias. Examples of these are sassafras pith (*Sassafras Medulla, Mucilago Sassafras Medullæ* U. S. P.), slippery elm ✓(*Ulmus, Mucilago Ulmi* U. S. P.), marshmallow root [illegible]*lthæa* U. S. P.), linseed✓(*Linum* U. S. P., B. P.), barley (Hordeum), sa[illegible] verbascum and quince seeds. Iceland moss is a lichen (Cetraria islandica), and contains starch bodies together with acids, which can be removed by soaking in dilute alkaline solutions for some time. Irish moss or Carragheen (*Chondrus* U. S. P.), a seaweed gathered on the coasts of Ireland and Massachusetts, contains a carbohydrate, carrageenin. The decoction forms a jelly when cold, and was formerly supposed to form a valuable food in illness, but it is of little value for this purpose, for only about $\frac{1}{20}$–$\frac{1}{30}$ of the jelly is solid matter, the rest water. Couch-grass, the rhizome of Agropyrum repens (*Triticum* U. S. P.) is used in the form of a decoction as a beverage in fever, and to dilute the urine. It has a certain popular reputation as a diuretic in suppression of the urine, calculus, etc., but this is entirely unmerited, for it increases the urine simply by the water given with it.

II. EMOLLIENTS.

Emollients are bland, oily substances which are applied to the skin to protect it from irritation, and to render it softer and more elastic, and thus bear the same relation to the skin as the demulcents to the mucous membranes. Their effect in rendering the skin softer and more pliable may be due in part to their penetration into the surface layers, but may also be explained by the slight congestion induced by the rubbing and massage used in their application.

Soften skin. Dissolve sebum of skin: rapid resorption of drugs. Substances in water for rapid resorption from m. m. In cuts, abrasions, etc + drug often

The older emollients were chiefly animal and vegetable fats and oils, but several newer drugs of this class are derived from petroleum. The effects of these drugs when applied to the skin are purely local. No doubt some small percentage is absorbed into the tissues, but this has no known effect in man, and although the fats and oils are valuable foods when taken internally, this plays no part in their effects when applied to the skin.

The emollient preparations promote the absorption by the skin of drugs dissolved in them, because they mix readily with the thin layer of oily sebaceous matter which covers it. The active substances dissolved in them therefore come into intimate contact with the absorbing cells lining the ducts of the glands, while watery solutions are separated from the living cells by a layer of sebum. If this layer be dissolved off by alcohol, watery solutions are also absorbed rapidly, and alcoholic solutions are absorbed as quickly as oily solutions, because the alcohol is miscible with the sebum. On the other hand solutions in water come into more intimate contact with the cells of the mucous membranes and with the subcutaneous tissues, and are therefore more readily absorbed by these than oily solutions. To ensure rapid absorption, a drug should be dissolved in some emollient if it is to be absorbed by the skin, in water when it is to be administered internally or hypodermically. Solutions in oil of such antiseptics as carbolic acid are much less powerful than those in water, because carbolic acid being more soluble in oil fails to diffuse into the watery protoplasm of the microbe, for which it has less affinity. (See Antiseptics of the Benzol Series.) But antiseptics which are more soluble in water than in oils are said to be equally active in both solvents.

The emollients are applied as protectives in abrasions, cuts, bruises, chapped hands, burns; they are less often used alone in extensive skin diseases, but are usually prescribed in these as the basis of ointments in which other remedies are incorporated. There is no question that the protection afforded to the part and the exclusion of the air by the oily emollient plays an important part in the action of these remedies, and it seems probable that in many cases equally good results would follow the application of the emollient without any active ingredient.

The emollient ointments are also applied to wounds and mucous membranes as protectives and also as vehicles for other remedies. Here they have a more lasting effect than watery applications, which are more readily absorbed. Emollients are seldom applied to the mouth because of their unpleasant oily taste, but the eye, nose, urethra, vagina and rectum are often treated with them.

PREPARATIONS.

✓ **Adeps** (U. S. P., B. P.), lard; the prepared internal fat of the abdomen of the pig, purified by washing in water, melting and straining.

✓ *Adeps Benzoinatus* (U. S. P.), *Adeps Benzoatus* (B. P.), benzoinated

Many become rancid + irritant.
Petrolatum liquidum dissolves drug for hypo as less pain than with H_2O

lard, is prepared from lard by the addition of benzoin, which is slightly antiseptic and preserves it from becoming rancid.

UNGUENTUM (U. S. P.), ointment, is a mixture of lard and yellow wax. It was formerly known as Unguentum Simplex, and is the basis of many other ointments.

Unguentum Diachylon (U. S. P.) is formed from lead plaster and olive oil, perfumed with oil of lavender. The lead is inert, the action being identical with that of ordinary ointment.

UNGUENTUM AQUÆ ROSÆ (U. S. P., B. P.), cold cream, is formed of spermaceti, white wax, oil of almonds, and some borax, scented with rose water.

Sevum Præparatum (U. S. P., B. P.), mutton suet, is obtained from the abdominal fat of the sheep.

Lard and suet have the ordinary constituents of animal fats, stearin, palmitin and olein. They are seldom used alone, but form the basis of numerous ointments. These animal fats tend to putrefy, and are then rendered irritant by the presence of free acids (rancidity), and have therefore been replaced to a considerable extent of late years by other preparations which do not suffer from this drawback.

Adeps Lanæ Hydrosus (U. S. P., B. P.), hydrous wool-fat, lanolin, the purified fat of sheep-wool, mixed with not more than 30 per cent. of water.

Adeps Lanæ (U. S. P., B. P.), wool-fat without water.

Lanolin has been used extensively in medicine only in the last few years. It consists of cholesterin esters with some impurities, does not become rancid, and differs from the older fats also in being miscible in twice its weight of water without losing its ointment consistency. Lanolin is very often used as an emollient application, as well as to form a basis for more active drugs.

Petrolates or **Paraffins.** When the more volatile constituents of petroleum are distilled off, there remain a number of higher hydrocarbons, chiefly of the marsh gas series, which are used in medicine as emollients. The lower of these hydrocarbons are fluid at ordinary temperatures and are known as

Petrolatum Liquidum (U. S. P.), *Paraffinum Liquidum* (B. P.), a colorless, oily transparent liquid without odor or taste. When these are removed there remains

PETROLATUM (U. S. P.) and PETROLATUM ALBUM (U. S. P.), PARAFFINUM MOLLE (B. P.), soft petrolate, vaselin, which has the consistency of an ointment, is yellow or white in color, and is liquefied a few degrees above the temperature of the blood. When the distillation is carried further, the residue is solid at ordinary temperatures, and is known as

Paraffinum (U. S. P.), *Paraffinum Durum* (B. P.), or hard paraffin, which melts at a somewhat higher temperature than vaselin.

Unguentum Paraffini (B. P.) is a mixture of three parts of hard paraffin with seven parts of vaselin.

By mixing the petrolates a salve of any desired consistency may be obtained. Soft petrolate is more extensively used than the others as an emollient and as a basis for ointments, and has the advantage over the older lard and suet that it does not become rancid. Liquid petrolate has been used to dissolve irritant substances for subcutaneous injection, as less pain is caused than when water is used.

Several **Oils** are also used as emollients.

Oleum Olivæ (U. S. P., B. P.), olive oil, a fixed oil obtained from the ripe fruit of the olive, Olea europæa.

Oleum Lini (U. S. P., B. P.), Linseed or Flaxseed oil.

Oleum Amygdalæ Expressum (U. S. P.), *Oleum Amygdalæ* (B. P.), a fixed oil expressed from bitter or sweet almonds. It is to be distinguished from the volatile oil obtained from the bitter almonds. The fixed oil contains no prussic acid.

no HCN

Oleum Gossypii Seminis (U. S. P.), Cotton-seed oil.

Olive oil protects ulcer of stomach from acid - wineglass before meals. Glycerine for chapped hands, soften scabs. Irritant action (2-5 cc & as suppositoria glycerini) cause peristalsis & mild purgation. [illegible]

Oleum Adipis (U. S. P.), oil of lard.

These all resemble each other in their composition, and may be used as emollients. Olive oil is generally preferred to the others, but is much more expensive, and it is probable that much of the so-called olive oil is really purified cotton-seed oil. Olive oil has been advised as a cholagogue, but has been shown by more exact methods of research to have no effect whatever on the secretion of the bile. It sometimes gives relief in biliary colic and dysentery and in some gastric disorders accompanied by pyloric spasm, probably from its acting as a protective to the mucous membrane of the stomach and duodenum. A wineglassful is given two or three times a day before meals; in these large doses it possesses a high food-value.

Cera Flava (U. S. P., B. P.), yellow wax. *Cera Alba,* white wax.

✓ **Cetaceum** (U. S. P., B. P.), spermaceti, obtained from the cachelot (Physeter macrocephalus), one of the whales.

These three preparations are not used alone, but are often added to the emollients and ointments in order to give them a firmer consistency, which is especially desirable in hot climates and in summer.

Ceratum (U. S. P.), a mixture of 3 parts of wax with 7 of lard.

Unguentum Cetacei (B. P.), is a mixture of white wax and spermaceti and olive or almond oil.

✓ **GLYCERINUM** (U. S. P., B. P.), Glycerin, a liquid obtained by the decomposition of animal or vegetable fats or fixed oils, and containing not less than 95 per cent. of absolute glycerin, $C_3H_5(OH)_3$; clear, colorless, of a syrupy consistence, oily to the touch, with a sweet taste and no odor, soluble in water and alcohol.

from decomp. of animal & veg. oils

Glycerin is used as a solvent for a number of other drugs, the preparations being known as *glycerites* (U. S. P.), *glycerines* (B. P.).

Glycerin is somewhat irritant to the unbroken skin, when it is applied in the pure form, and even diluted glycerin causes pain and smarting when it is applied to unprotected surfaces such as cuts or burns, but the pain soon disappears, and glycerin then acts as a protective. The irritation is due to the glycerin abstracting the fluids of the tissues owing to its avidity for water. Glycerin and its preparations are used very extensively as applications to slight wounds, in irritation of the skin and lips from exposure to cold, and in similar conditions. They are often applied to hard, dry crusts on the skin in order to soften them and permit of their removal.

The irritant action of glycerin causes peristalsis and evacuation of the bowels when small quantities are injected into the rectum; the stool is of almost ordinary consistency, and no pain or colic is felt subsequently, nor does the remedy cause more than one evacuation Glycerin may be injected into the rectum for this purpose (dose 2–5 c.c., ½–1 teaspoonful), but a more convenient form is the glycerin suppositories, **Suppositoria Glycerini,** which are made up with stearic acid and sodium carbonate, U. S. P., with gelatin, B. P. These suppositories are found not to keep well, as the glycerin tends to attract moisture and then escapes; to avoid this they are often encased in paraffin, which is broken off immediately before they are inserted. Glycerin suppositories are used in constipation instead of the ordinary aperients. Large doses of glycerin taken internally sometimes cause purgation, but it is not a reliable remedy when administered in this way.

Dusting powders to soak up fluids = crust - best protection
Talc Starch

Glycerin in large quantities is poisonous whether it is taken by the mouth or injected hypodermically or intravenously. It is true that no case of glycerin poisoning in man is known, but large doses are fatal to animals in the course of a few hours. The chief symptoms are restlessness, agitation, acceleration of the heart and respiration, general weakness, tremor and convulsions, which finally end in somnolence, coma, and death from failure of the respiration. The convulsions are marked only after large doses, when they may assume a tetanic character. A rise in the temperature has been noted by several observers, followed by a fall which continues until death. Glomerulonephritis has also been observed in animals. Glycerin is absorbed rapidly from the intestine, and undergoes combustion in the tissues, only a very small fraction of it reappearing in the urine.

It follows from the fact that glycerin is oxidized in the tissues that it must supply the body with energy and act in some sense as a food. This is of interest chiefly because, the ordinary fats being compounds of glycerin, a certain amount must be contained in the food, but it is also of some therapeutic importance, because glycerin has been advised as a food in inanition, and has even been said to rival cod-liver oil. In respect to its value as a food, glycerin resembles ordinary alcohol, being readily absorbed, and undoubtedly increasing the total energy of the body.

Glycerin has been said to have some effect on the sugar formation in the tissues. In some forms of experimental glycosuria, apparently less sugar is found in the urine if glycerin be administered, and in a certain number of cases of diabetes in the human subject, some improvement is said to have occurred under glycerin treatment. No satisfactory explanation of this point has been offered. Quite apart from its supposed action on diabetes, glycerin has been used as a substitute for sugar in this disease, but its place has been taken of late years by saccharin.

Glycerin has been shown to possess some virtue as an antiseptic, probably from its withdrawing water from the microbes, but like the oils (page 49) it is a less suitable solvent for many antiseptics than water.

Along with the emollients, or oily protectives, may be mentioned another class of mechanical agents, the **Dusting Powders.** Any dry, insoluble, fine powder applied to irritated surfaces of the skin, or slight abrasions, will protect these from the air, and from contact with the clothes and other sources of pressure. These powders, at the same time, soak up any secretions, and render the injured spot less liable to bacterial infection, as they form a more or less impermeable crust. Powders used for this purpose should not be absorbed, or, if absorbable, should not induce any toxic effects. Those most commonly employed are the phosphate and carbonate of lime, talc (*Talcum, Talcum Purificatum,* U. S. P.), (magnesium silicate), fullers' earth and kaolin (aluminum silicates), starch, and *Lycopodium* (U. S. P.), which consists of the spores of Lycopodium clavatum (club moss).

A large number of powders are used as surgical dressings, most of them being credited with more or less antiseptic power. In many instances, however, their antiseptic action is so slight that it would appear that most of their virtues are due to their mechanical properties, and not to their bactericidal action.

III. SUGARS AND FLAVORING SUBSTANCES.

Sugars are used in medicine chiefly to disguise preparations of unpleasant taste, and in the small quantities usually employed have little further effect. In large quantities sugars, like other diffusible bodies, act as irritants to the stomach and bowel, and comparatively small quantities of some sugar substances possess an aperient action. Thus molasses and imperfectly refined sugar have some reputation in domestic medicine as aperients, and honey, manna, Cassia fistula, and several fruits are included as mild laxatives in the pharmacopœias. They are scarcely prescribed alone in medicine, but are used to give bulk to preparations of the stronger purgatives, such as senna. Their aperient action seems to be due to their colloid form, as pure sugar has no such effect, and it is possible that they merely delay the absorption of fluid, and thus cause softer evacuations than would otherwise occur.

PREPARATIONS.

Saccharum (U. S. P.), **Saccharum Purificatum** (B. P.), cane sugar.

SYRUPUS (U. S. P., B. P.), a concentrated solution of sugar. Syrup is the basis of a large number of medicated syrups of the pharmacopœias. Sugar and syrup are used exclusively to sweeten mixtures and to aid in the suspension of insoluble bodies. In place of ordinary syrup many of the flavored preparations may be used, such as syrup of citric acid, of acacia, of almonds, etc.

Saccharum Lactis (U. S. P., B. P.), sugar of milk, lactose, is not so sweet as ordinary sugar, and is much less liable to deliquesce, so that it is used largely to give bulk to powders. It has been said to have diuretic properties when given with large quantities of water, and to cause purgation when given in a more concentrated solution. Asses' milk contains more lactose than cows' milk, and has been recommended for its slight aperient action in chronic constipation.

Bulk to
powders

Maltum (U. S. P.), malt, barley grain partially germinated and then dried.

Extractum Malti (U. S. P.). Dose, 16 c.c. (4 fl. drs.).

Mel, honey, and *Mel Depuratum* (U. S. P., B. P.), or clarified honey, are used to give taste to mixtures, and have a very slight aperient action, so that they may be advised as articles of diet in habitual constipation. Some medicated honeys are used, of which *Mel Rosæ* is included in the U. S. P., *Mel Boracis* in the B. P.

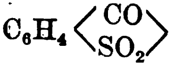
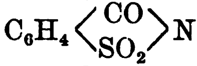
Oxymel (B. P.) is a mixture of honey and acetic acid. Dose, 1–2 fl. drs.

Syrupus Glucosi (B. P.), a mixture of liquid glucose and syrup.

A number of saccharine preparations with a slight aperient effect are ingredients of the preparations of the more powerful purgatives. Thus manna (*Manna* U. S. P.) obtained from the flowering ash, is contained in the Infusum Sennæ Co. U. S. P., and purging Cassia (*Cassia Fistula,* U. S. P., *Cassiæ Pulpa,* B. P.), tamarinds (*Tamarindus,* U. S. P., B. P.), figs (*Ficus,* U. S. P., B. P.) and prunes (*Prunum,* U. S. P., B. P.) form constituents of the confection of Senna and other preparations.

They are not prescribed alone, but the fruits may be advised as articles of diet where a mild laxative is required. The tamarind pulp may owe its aperient action in part to the presence of tartrates, citrates, malates and other cathartic salts. (See Saline Cathartics.)

Frequently other flavors are preferred to sugar, which is especially disliked in fever cases, as sweet fluids do not quench the thirst so effectually as acids and bitters. Many of the preparations of the volatile oils and some of the demulcents are used almost exclusively as flavoring agents, and in some both sugar and volatile oil are combined, as in the syrups.

Instead of sugar some artificial compounds have been introduced of late years. **Glusidum** (B. P.), **Benzosulphinidum** (U. S. P.), or **Saccharin**,  $C_6H_4\left\langle\begin{matrix}CO\\SO_2\end{matrix}\right\rangle NH$, and its sodium salt,  $C_6H_4\left\langle\begin{matrix}CO\\SO_2\end{matrix}\right\rangle NNa$, or soluble saccharin are the best known of these. Saccharin is a light, white crystalline powder, soluble in 400 parts of water and in 25 parts of alcohol. It is about 500 times as sweet as sugar, and gives a distinct flavor to 70,000 times its weight of water. It does not taste exactly like sugar, however, there being a distinct flavor besides that of sweetness, and patients generally object to it after a short time. They have been used as substitutes for sugar in diabetes, a disease in which sugar is to be avoided as far as possible. Some writers state that in the presence of saccharin the digestive ferments act more slowly than usual, but the retardation is only trifling and does not preclude the use of saccharin in the small quantities necessary to sweeten the food. Even very large doses of saccharin may be injected intravenously in animals without other effect than some depression and stupor.

Some pharmacopœial preparations are designed to give color to solutions, but are seldom or never prescribed, although they are sometimes added by the pharmacist.

Among these are cochineal (*Coccus,* U. S. P., B. P., *Tinctura Cocci,* B. P.) and saffron (*Crocus,* B. P.).

IV. SIMPLE BITTERS.

This group includes a number of substances which have little in common except their bitter taste and their comparative inactivity in the body. Several alkaloids may be placed in it, *Berberine, Buxine, Menispermine* and *Canadine,* for, although these are poisonous in very large quantities, they are harmless in those in which they are contained in the preparations used in therapeutics. In addition to these there may be placed in it numerous neutral bodies, possessing an intensely bitter taste, but with little or no further action, such as the *Quassiins, Columbin,* and a few weak acids and glucosides.

Pharmacological Action.—These substances, or rather the preparations containing them, are largely used in therapeutics in order to increase the appetite, and their administration is often followed by a distinct improvement in the digestion and an increase in weight.

Alimentary Tract.—These effects are explained by the action of bitter substances in increasing the secretion of gastric juice, which has been shown to occur in man and animals by a number of experiments. This is not, however, through the bitters acting on the gastric mucous membrane directly, for when they are applied through a gastric fistula, they have no specific action on the secretion. Pawlow has

Increase psychical secretion if just before meal
Only when gastric juice deficient

shown that the chief factor that determines the activity of the gastric secretion is the odor and taste of food; thus in dogs with œsophageal fistulæ, in which the food swallowed does not pass into the stomach but escapes through a wound in the œsophagus, the taste and odor of food cause a profuse secretion of gastric juice (psychical secretion). Bitters given shortly before augment this reflex, and the same effect is seen when the mouth is merely rinsed with bitter solution. The action of the bitters is therefore to increase the psychical secretion of gastric juice, possibly because of the contrast offered by the bitter and the pleasant tastes. The inference may be drawn that the therapeutic effects are best elicited when the bitters are given shortly before a meal, and this accords with universal experience. And the use of the bitters is attended with benefit only in cases in which the gastric juice is deficient. The increase of the gastric juice is followed as usual by a more active secretion by the pancreas. In addition, it is to be remembered that the improvement is largely subjective, and that the bitters are capable of producing a considerable impression upon patients, so that the effects may be due in part to suggestion and not to any real action of the drug.

In comparison with their effects on secretion, the other changes induced in the alimentary tract by the bitters are insignificant. They have little or no effect on the activity of the ferments in themselves but the tannin and colloids of the usual preparations may retard their action. And they do not affect the growth of bacteria or yeasts. Absorption from the alimentary tract and the movements of the stomach and bowel are not altered by their presence. The salivary secretion is generally augmented by bitter tastes and some increase in the leucocytes and red cells of the blood is said to occur after their use.

Action after Absorption.—In very large quantities some of the bitters produce effects that are obviously due to their absorption. These have seldom been observed in man, but have been studied in animal experiments. Thus Compardon states that in many individuals 0.12 G. of *quassiin* produces burning in the throat and stomach, discomfort, headache, nausea, and vomiting. In flies and other insects it has a narcotic action. *Columbin* and *cetrarin* were found by Köhler to increase the blood pressure by stimulation of the vasomotor centre when they were injected intravenously. Ramm states that the intravenous injection of cetrarin causes irritation of the stomach and bowel, purging and vomiting, and general paralysis of the central nervous system, which is preceded by convulsions in mammals. He did not observe any increase in the blood pressure. Both the glucosides of *condurango* produce in dogs ataxia and loss of coördination, with increased movement, and eventually convulsions, and death follows in 12–72 hours or longer. The brain seems the part chiefly affected in mammals, although the reflex excitability of the spinal cord is also augmented in the frog (Jukna). *Buxine* possesses considerable antiseptic power, and prevents the movement of leucocytes and of the lower organisms in the same way as quinine. Large doses often cause vomiting, confusion, giddiness and tremor, with diarrhœa in dogs, but are sometimes without effect. *Aristolochine,* which has been found in several species of Aristolochia, and probably occurs in the official serpentary, produces in rabbits acute necrotic nephritis, with albuminuria and uræmic symptoms. In dogs it causes a very marked fall of blood pressure, and hemorrhages in the intestinal mucous membrane, but no nephritis. The poisonous action of aristolochine is very similar to, but much more powerful than that of aloin (Pohl). *Lupulinic acid* obtained from hops, when injected as a neutral salt into the blood, causes first stimulation and then paralysis of the medullary centres, but has very little effect when given by the stomach even in large doses (Dreser). In beer an oxidized product of lupulinic acid occurs, which has no effect even when injected into the blood. *Berberine* is a very widely distributed alkaloid of the pyridine series ($C_{20}H_{17}NO_4$), and when administered in very large quantities per os, causes diarrhœa, and occasionally vomiting, tremor, acceleration of the pulse and respiration and general weakness, from which the animal recovers only slowly. Its subcutaneous or intravenous injection is followed by the same symptoms, but paralysis of the hind extremities, convulsions, and asphyxia from failure of the respiratory centre may occur when it is administered in this way, while the largest quantities are not fatal when exhibited by the stomach. The acceleration of the pulse seems due to paralysis of the inhibitory terminations in the heart, and is accompanied by a fall of blood pressure from the effects of the alkaloid on the vasomotor centre and on the heart directly. Berberine has been credited with causing contraction of the uterus and of the spleen, but this is disputed. It has also been said to resemble quinine in its effects on bacteria and on the leucocytes, but only in very strong solution. Berberine seems to be excreted in part by the kidney unchanged, and is said to cause nephritis in large doses.

The *cotoin* of Coto bark, and the *paracotoin* and other constituents of Paracoto bark are said to cause dilatation of the intestinal vessels when they are injected intravenously or perfused through the mesenteric vessels. Paracotoin is much weaker than cotoin.

Orexine ($C_{14}H_{12}N_2$), an artificial base, seems to stand midway between the peppers and the bitters in its action, as it is somewhat more irritating than most of the latter. Injected into the frog it induces paralysis, which is apparently of peripheral origin, and its subcutaneous application in mammals is followed by tremor, tonic and clonic convulsions, dyspnœa, acceleration of the heart and vomiting. It has some antiseptic action, and tends to form methæmoglobin when mixed with the blood. No symptoms have been observed from its use in man, except increased appetite and augmentation of the gastric secretion, and in a few cases a feeling of heat in the throat and some nausea.

PREPARATIONS.

Gentiana (U. S. P.), **Gentianæ Radix** (B. P.), gentian, the root of Gentiana lutea, contains a glucoside, gentiopicrin, a neutral body, gentisin, and a trace of tannic acid. 1 G. (15 grs.).

0.1 - .5 g Extractum Gentianæ (U. S. P., B. P.), 0.1–0.5 G. (2–10 grs.).

½ - 2 cc *Fluidextractum Gentianæ* (U. S. P.), 0.5–2 c.c. (10–30 mins.).

2-16 cc Tinctura Gentianæ Composita (U. S. P., B. P.), containing gentian, bitter orange peel, and cardamom, 2–16 c.c. (½–4 fl. drs.).

Infusum Gentianæ Compositum (B. P.), containing gentian, bitter orange peel, and fresh lemon peel, ½–1 fl. oz.

Quassia (U. S. P.), **Quassiæ Lignum** (B. P.), the wood of Picræna excelsa, contains several neutral bitter substances, resembling each other closely chemically and known as quassiins.

Extractum Quassiæ (U. S. P.), 0.05–0.2 G. (1–3 grs.).

Fluidextractum Quassiæ (U. S. P.), 0.5–2 c.c. (5–30 mins.).

1 - 4 cc Tinctura Quassiæ (U. S. P., B. P.), 1–4 c.c. (15–16 mins.).

Infusum Quassiæ (B. P.), ½–1 fl. oz.

Calumba (U. S. P.), **Calumbæ Radix** (B. P.), columbo, the root of Jateorrhiza palmata, or Columba, contains columbin, a neutral body, columbic acid, and the alkaloid berberine.

Fluidextractum Calumbæ (U. S. P.), 1–2 c.c. (15–30 mins.).

4 - 16 cc Tinctura Calumbæ (U. S. P., B. P.), 4–16 c.c. (1–4 fl. drs.).

Infusum Calumbæ (B. P.), ½–1 fl. oz.

Chirata (U. S. P., B. P.), Chiretta, the plant Swertia chirata, contains a glucoside, chiratin, and ophelic acid.

Fluidextractum Chiratæ (U. S. P.), 0.3–1 c.c. (5–15 mins.).

Tinctura Chiratæ (B. P.), 4–8 c.c. (1–2 fl. drs.).

Infusum Chiratæ (B. P.), ½–1 fl. oz.

Taraxacum (U. .S. P.), the root of the dandelion, Taraxacum officinale, contains two neutral bitter substances.

Extractum Taraxaci (U. S. P.), 0.3–1 G. (5–15 grs.).

Fluidextractum Taraxaci (U. S. P.), 4–12 c.c. (1–3 fl. drs.).

Berberis (U. S. P.), barberry, the rhizome and roots of various species of Berberis, contains berberine and tannin, 2 G. (30 grs.).

Fluidextractum Berberidis (U. S. P.), 2 c.c. (30 mins.).

Pareira (U. S. P.), the root of Chondrodendron tomentosum, contains an alkaloid, buxine.

Fluidextractum Pareiræ (U. S. P.), 2–8 c.c. (½–2 fl. drs.).

Serpentaria (U. S. P.), snake-root, the rhizome and roots of Aristolochia serpentaria and of Aristolochia reticulata, contains a volatile oil, an unknown bitter principle, and perhaps an alkaloid, aristolochine.

Fluidextractum Serpentariæ (U. S. P.), 1–2 c.c.

Tinctura Serpentariæ (U. S. P., B. P.), 2–8 c.c. (½–1 fl. dr.).

Humulus (U. S. P.), hops, the strobiles of Humulus lupulus, and **Lupulin**, a glandular powder separated from hops, contain a volatile oil, a bitter neutral substance, lupulin, lupulinic acid, and resins.

Fluidextractum Lupulini (U. S. P.), 2–8 c.c. (½–2 fl. drs.).

Oleoresina Lupulini (U. S. P.), 0.1–0.3 G. (2–5 grs.).

Cusparia or Angostura bark, the dried bark of Cusparia febrifuga, contains four or more alkaloids, cusparine, cusparidine, galipine, and galipidine, along with a volatile oil and a neutral bitter stuff.

Nectandræ Cortex, Bebeeru bark, contains an alkaloid which is now known to be buxine, but which has been called beberine, biberine, or bebeerine hitherto.

Condurango, the bark of Gonolobus condurango, contains two glucosides of similar properties, and has been used a good deal of late years as a stomachic bitter. It was formerly credited with a specific action on epithelioma.

Cetraric acid, or cetrarin, is obtained from Iceland moss (see page 48), and has been recommended as a bitter in doses of about 0.1 G. (2 grs.), in tablets.

Coto bark, whose origin is still doubtful, contains cotoin ($C_{22}H_{18}O_6$), and has been used to form a fluid extract. Dose, 0.3–1.5 c.c. (5–20 mins.). Cotoin has been prescribed in the dose of 0.03–0.2 G. (½–3 grs.).

Orexine Hydrochlorate, $C_6H_4N_2C_2H_3C_6H_5HCl$, is a colorless, crystalline body, soluble in about 15 parts of water, with a bitter, somewhat pungent taste. It is prescribed in powder or tablets. Dose, 0.3 G. (5 grs.).

Bael fruit, or Bengal quince, was formerly contained in the B. P., but has been omitted in the last edition. Very little is known regarding its action or principles, but it may perhaps have some effect as a bitter.

Many other bitter stomachics might be enumerated, some of which have been used largely in former times, but as they are all identical in their effects, it seems unnecessary to do so.

Instead of the simple bitters, cinchona and nux vomica preparations are often used in small quantities. Many of the preparations which will be enumerated under the volatile oil series owe much of their effect to the bitter which accompanies the volatile oil, and in numerous other pharmacopœial preparations bitters are present, although their effect is hidden by the action of the drug in other directions.

Therapeutic Uses.—The bitters are used chiefly to increase the appetite and the digestion. In convalescents, in persons of sedentary habits, and occasionally in chronic dyspeptic conditions they are of value, while in cases of more acute gastric irritability and in hyperacidity they may do harm rather than good. Gentian, Quassia, Calumba and Chirata are the only simple bitters that are largely used, and the first is much the most important. They are generally prescribed as tinctures, fluid extracts or other fluid preparations. The last three may be prescribed with iron preparations, as they contain little or no tannic acid and thus cause no precipitate. Pills are sometimes prescribed with extract of gentian or quassia, but it seems open to question whether these ingredients have really any effect when given in this form, as the bitter taste, on which their action depends, is largely concealed. Compound tincture of gentian is sometimes used to give flavor rather than for any effect on the digestion.

Quassia infusion (ten per cent.) is injected as an enema in the round worms of children.

Several of the drugs mentioned, such as taraxacum and gentian, have been supposed to have a specific action on the liver, but there are no sufficient grounds for this belief. The supposed virtues of pareira as a diuretic and of berberine, buxine, and other alkaloids as substitutes for quinine in malaria have also proved to have no foundation, and the popular reputation of hops as a narcotic probably arises from its association with alcohol in beer. Cotoin and Coto bark are said to have some special effect in lessening diarrhœa, in addition to their action as bitters.

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V. VOLATILE OIL SERIES.

The group of volatile, ethereal, or essential oils contains a large number of preparations in the pharmacopœias of all countries. These oils are obtained from plants by distillation, or more rarely by pressure, and must be distinguished by the student from the fatty

Vol oils from fruits & flowers. Odor - Mostly terpenes $C_{10}H_{16}$
slightly sol in H_2O: aquae.

or fixed oils, which are non-volatile. The volatile or ethereal oils are found chiefly in the fruits and flowering parts of plants, and are very widely diffused through the vegetable kingdom, though some orders, such as the Labiatæ, Umbelliferæ, Aurantiaceæ, Cruciferæ, and Coniferæ, are preëminent in their production. They are all strongly odorous, and are therefore used in perfumery, and to conceal nauseous odors and tastes in medicine.

Their composition is extremely variable. The commonest constituents are *Terpenes*, and some oils contain these only, while in a few oils no terpene has been found (Attar of Roses). Terpenes are hydrocarbons of the aromatic series, and possess the general formula $(C_5H_8)_n$. The great majority of them, or the terpenes proper $(C_{10}H_{16})$, are combinations of a dihydrobenzol with propyl and methyl $(C_6H_4(H_2)C_3H_7CH_3)$. Some twelve terpenes of this formula are known, varying in their chemical structure and in their stereometrical form. Another group of these hydrocarbons is formed by the *Sesquiterpenes* $(C_{15}H_{24})$, while a few *Diterpenes* $(C_{20}H_{32})$ are known. Some volatile oils consist of these hydrocarbons only, but many of them contain in addition some oxidized aromatic substances, such as phenols, ketones, aldehydes, acids and their compounds; as instances of these may be cited camphor, thujon (from oil of absinth), sabinol (oil of savine), safrol, thymol, eucalyptol, myristicin and vanillin. Many of these oxidized products crystallize out when the volatile oil is cooled sufficiently, and especially on long standing, and the resulting solid is known as a *Stearoptene*, while the fluid remaining is sometimes called *Elæoptene*. The oils containing oxygen are not so volatile as the pure hydrocarbons, but the odor is often due chiefly to the oxidized substances. A very few oils contain nitrogenous bodies, generally in the form of cyanides, while, on the other hand, the majority of the volatile oils of the Cruciferæ contain sulphur bodies, which lend them a pungent disagreeable odor, quite different from that of the other oils.

The volatile oils are generally clear, colorless fluids, although some of them are green from the presence of small quantities of vegetable coloring matter, while others are blue in color from the presence of a terpene derivative (azulene). After long keeping they often acquire a yellowish color and an acid reaction, from the formation of resins. They are generally light, sparkling fluids, but the oils of copaiva and cubebs are more viscid. They are insoluble in water except in very small amount, which, however, is enough to lend their characteristic odor to the solution; in strong alcohol, ether, benzol, chloroform, and fixed oils, they are freely soluble.

Many of the plants from which the volatile oils are obtained possess other active constituents, such as bitters, and as many of the preparations used in therapeutics are formed, not from the distilled oils, but from the crude parts of plants, it must be noted that the oil is not the only active principle in them. A series containing members which differ so widely chemically, and which in fact have only their volatility and their aromatic nucleus in common, could not be expected to have a uniform action in the animal organism. It is found, however, that they resemble each other in their therapeutic properties, because they are used almost solely for their local action, and that in only small quantities.

Antiseptic, irritation, dil of vessels, warmth, increased secretion, increased peristalsis & gas → (carminatives), psychic on gastric secretion. In elimination increased bronchial effects; diuretic & antiseptic. Nervous effects.

Skin = redness, itching & warmth. Penetrate cells & then foreign bodies = antiseptic action

Action Externally.—The volatile oils all possess antiseptic properties, which are doubtless due in part to their volatility enabling them to penetrate readily into protoplasm and to lessen its vitality by acting as foreign bodies. In addition, they are nearly related to the benzol series, the members of which are all antiseptics and protoplasm poisons. They differ a good deal in their germicidal power, and are much more poisonous to the moulds than to the bacteria. The terpenes are not generally so strongly antiseptic as the other constituents, and these last vary much in their activity, as well as in their relative amount in the oils.

Their volatility may also explain their irritant action in part, for most other volatile substances are more or less irritant, but here again their relation to the phenols and benzol cannot be ignored. Applied to the skin, they cause redness, itching and warmth, owing to a local dilation of the vessels, which may be due to the penetration of the oil to the cutaneous arterioles or veins, or to a reflex from the irritated terminations of the sensory nerves acting on the vasomotor centres.

When painted on the mucous membranes, such as those of the eye or nose, or on wounds, the volatile oils cause similar irritation, which is betrayed by redness and congestion, pain and smarting.

Action on the Alimentary Canal.—Strong solutions of the oils act as irritants in the mouth. They have generally a hot, burning taste, and if kept in the mouth, cause redness and irritation of the mucous membranes, although some of them induce a sense of coolness at first. At the same time the organs of smell are affected by these oils, which are almost all possessed of characteristic odors. The irritation of the mouth leads to a reflex secretion of saliva, which is often very profuse. The antiseptic action of the oils is exercised in the mouth as elsewhere, and may have a beneficial effect in some conditions.

On passing into the stomach, the oils cause the same sensation of warmth in that organ, and this is accompanied by a sense of well-being and comfort, the appetite is often increased, and any feeling of distention after meals is relieved. This is often attended by the eructation of quantities of gas. Substances which produce these effects in the stomach are known as *carminatives*, and many explanations of their action have been offered. The oils undoubtedly act as antiseptics here as elsewhere, and may hinder the development of yeasts and other organisms and thus be of benefit, but this would not give the immediate feeling of relief which is often experienced after a small quantity of these remedies. The process of digestion seems to be rather retarded than accelerated by the presence of the oils, as far as can be judged by test-tube experiments and by some measurements made by Buchheim on the digestion of animals with gastric fistulæ. The secretion of the gastric glands has been said to be increased by the direct action of the volatile oils, but this has been disputed. But it must not be forgotten that the most powerful stimulant to gastric secretion is the smell and taste of food, and that substances of agree-

Accelerate movements of stomach – carminatives.
Reflex dil of vessels increase saliva
Excreted: comp. sulphates, glycuronates (+ acid + Fehling's positive). breath skin.

able taste and odor cause a marked increase in the gastric juice by reflexes from the mouth and nose. The eructation of gas certainly suggests that the volatile oils accelerate the movements of the stomach, and this has been repeatedly confirmed by the direct observation of the stomach walls. Brandl has also shown recently that absorption occurs much more rapidly from the stomach in the presence of slight irritants, such as the volatile oils. Finally it must be added that many of the beneficial effects are purely subjective; the patient has a feeling of warmth and comfort in the region of the stomach, arising from the slight irritation and consequent hyperæmia of the mucous membrane, but this does not necessarily indicate any marked alteration in the processes of digestion or in the movements of the stomach.

Similar effects are believed to be produced in the intestine, for the administration of these oils is often followed by an improvement in its condition, manifested by lessened flatulence and distention, and relief is given by their use in some forms of colic. The antiseptic action may play a part in these effects. Scanzoni and Farnsteiner have recently shown that the intestine, like the stomach, absorbs more rapidly in the presence of small quantities of the oils. Whether the peristaltic movements of the bowel are increased is quite unknown. It is believed, however, that their administration lessens the pain and griping produced by some of the more powerful purgatives, and several pharmacopœial preparations are formed on this theory, which is supported by many years of clinical experience.

A considerable increase in the leucocytes of the blood follows their ingestion by the mouth, but this is observed in congestion of the stomach and intestine from other causes and is not induced by the subcutaneous or intravenous injection of the volatile oils, so that it cannot be regarded as a specific effect. Winternitz found that irritation of the pleura causes less purulent exudate in animals treated with some volatile oils than in controls which were not treated in any way, and concludes that the presence of the oils in the blood lessens the exudate and also promotes its absorption; he is inclined to regard this antiphlogistic action as a result of the leucocytosis and of a supposed attraction exercised on the leucocytes by the oils, which prevents their wandering into the tissues.

Excretion.—Like other bodies of the aromatic series, they tend to undergo a partial oxidation in the body; thus the terpenes ($C_{10}H_{16}$) become terpenols ($C_{10}H_{15}OH$), and several derivatives of the terpenes have been shown to undergo a similar change of a hydrogen atom to hydroxyl, while others which contain the -OH group originally, remain unaltered. The odor of the original oil or of these derivatives may often be detected in the breath, showing that a small part is excreted by the lungs, and possibly traces may be eliminated by the skin. Some also escapes by the kidney uncombined and imparts an odor to the urine either of the original oil or of some oxygen derivative; for instance, oil of eucalyptus or of turpentine gives the

{bronchial secretion. diuretic action.
excess – violent irritation of G.i. tract. hyperaemia etc (v)

urine a violet odor. But much of the hydroxyl product is combined with glycuronic acid and escapes in the urine in this form, while some may combine to form conjugate sulphates. The glycuronic acid reduces Fehling's solution, especially when the urine is previously boiled with acid, so that the volatile oils were formerly credited with inducing glycosuria. Some of the constituents of the oils are oxidized to acids and excreted in the urine as salts.

In the course of excretion, some of the oils cause irritation of the lungs and kidneys, so that some of them are employed to increase the bronchial secretion, while others have a distinct diuretic action. This irritant action is of course not confined to the tissue, but extends to microbial guests, so that some of the volatile oils are given internally almost exclusively for their antiseptic action in the urine.

Poisoning.—The various oils differ a good deal in their activity, while resembling each other closely in the general characters of their effects. All of them may produce marked irritation of the stomach and bowel when given in large quantities, but the oils of tansy, sage, and English pennyroyal are distinguished especially by the violent inflammation they cause, and by the frequency with which fatal poisoning occurs from their use. The terpenes appear to be but slightly poisonous, and their effects are probably limited to local irritation; the oxidized aromatic substances have been shown to be the poisonous constituents in all the oils hitherto examined. The symptoms are those of acute gastric, intestinal, and often renal irritation—vomiting, purging, acute pain in the abdomen, blood in the stools and in the vomited matter, collapse, weakness of the pulse and respiration, anuria, or albumin and blood in the urine, and convulsive attacks ending in coma and death. Great hyperæmia of the abdominal organs, often blood in the peritoneal cavity, and sometimes acute inflammation of the kidney are the chief post-mortem appearances. The hyperæmia and congestion of the organs of the abdomen may cause abortion in pregnancy, or increase the menses, and in the majority of cases of poisoning, these oils have been taken with the object of inducing abortion. In many instances, however, the drug has proved fatal without this end being achieved.

General Action.—The small quantities of volatile oils administered in ordinary medicinal use pass through the tissues without modifying them perceptibly, their only effects arising in the organs by which they are absorbed and excreted. In large quantities, however, some of them (the oils of wormwood, nutmeg, sage, savine among others) produce symptoms which indicate an affection of the central nervous system quite apart from their local action. The latter also produces nervous effects reflexly, and it has been found exceedingly difficult to distinguish these indirect results from those caused by the direct action on the central nervous system. A good deal of divergence is to be found in the statements of different writers from this cause, and also from the fact that comparatively few researches have been carried out with pure principles. Many of the oils vary in their constituents according to the climate, the season of the year, and other conditions under which the plant was grown, and some of the confusion may arise from differ-

first nervous excitement then depression.
Th: flavor, carminative, (antiseptic, expectorants) Also malodorous oils. G.u. disinfectants & skin irritants

ences in the oils used by investigators. Almost all the oils hitherto examined cause depression and final paralysis in the *frog*. The action seems to be mainly on the brain, larger quantities being required to paralyze the spinal cord than to prevent all spontaneous movements. This stage of depression is preceded by one of excitement after oil of wormwood and some others. Some of the oils paralyze the terminations of the motor nerves in voluntary muscle like curara and camphor.

In ***mammals*** the general action of the constituents of the volatile oils seems to involve a preliminary stimulation and subsequent depression of the nerve cells. The relative importance of these two stages differs in different oils, some, *e. g.*, turpentine oil, causing only a transient excitement, followed by marked weakness and depression, while others, such as the oil of absinth, cause very marked excitement and convulsions. The activity of the oils as nervous poisons also varies greatly, some producing only insignificant effects on the central nervous system compared with those from their local action, while in others, such as the oil of absinth or wormwood, the symptoms from the nervous system predominate in cases of poisoning. As a general rule the higher divisions of the central axis are affected more than the lower, and epileptiform or clonic convulsions may be induced (camphor), or tremors similar to those described under carbolic acid and presumably of similar origin (safrol and nutmeg oil). In many cases a combination of excitement and ataxia is observed, the animal moving about restlessly, but being unable to balance itself. In the later stages of poisoning the spontaneous movements cease, while the excitation of the lower centres still persists, and wild convulsive movements accompany the final arrest of the respiration.

The ***medullary centres*** are also affected differently by the various oils and their constituents. The respiration is finally depressed by all of them, but this depression is often preceded by stimulation, the breathing increasing both in rapidity and in volume. The vasomotor centre undergoes similar changes, the blood-pressure falling from some oils immediately, from others only after a preliminary increase.

small dose: r. constriction so blood pres. up. large dose inhibits heart besides. So pressure down

The ***heart*** does not seem to be affected by most of the volatile oils, except indirectly. In cases of poisoning the collapse and shock may alter the character of its contractions, but direct effects on the cardiac muscle have not been shown to be produced by the volatile oils, unless when enormous quantities are injected intravenously.

Some of the constituents of the oils (pulegon, myristicin, safrol) cause fatty degeneration of various organs, especially of the liver and kidney, while others of very similar constitution have no such effect.

Although these general effects of the volatile oils have no therapeutic importance, the frequent occurrence of epilepsy and insanity in habitual absinth drinkers and occasional poisoning from others of the series have given them some practical interest.

Different oils are used for different purposes in therapeutics, although they all resemble each other in most respects, and it is, therefore, convenient to divide them into several therapeutic classes.[1] A number of the less irritant members are used very largely as flavoring agents, for their carminative effects on the stomach and intestine, more rarely as antiseptics, and as expectorants. Another small class may be formed of the malodorous oils, a third of those used as genito-urinary disinfectants, while several which are too irritant to be employed as carminatives, will be discussed among the skin irritants.

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[1] Two small and unimportant groups of bodies which are used for the same purposes as some of the volatile oils have been inserted along with these.

Carminatives only where no irritation - where not enough juice
oil of cloves - paralyzes exposed dental nerve

1. Volatile Oils Used as Flavoring Agents and Carminatives.

As regards their use as flavoring agents but little need be said, one preparation is used by one physician, another by another, and the selection is largely a matter of custom and taste. The orange preparations are probably more generally appreciated by patients than any others. Carminatives are used only when no marked irritation of the stomach or intestine is present, in cases where the gastric juice seems unable to cope with the food ingested, especially in persons of sedentary habits. In cases of colic, flatulence and abdominal distention they are often of use, provided that these are not due to peritonitis and other inflammatory diseases. Several of them have been employed as surgical antiseptics, notably thymol, but its insolubility in water has prevented its extensive adoption; they are more widely used as parasiticides for scabies, pediculi, etc. Some of the oils, such as oil of cloves, are used in dentistry to relieve pain, and also for their antiseptic action; the relief of pain is due to their paralyzing the exposed nerve ends after a preliminary irritation. Eucalyptus has been advised in septic conditions and in malaria, and at one time was supposed to be a specific for the latter; it improves some cases, but is not reliable, and has probably no more effect than others of the series. Its use as an internal remedy in septicæmia is apparently no more successful, although it still enjoys some reputation in these cases. Volatile oil preparations are sometimes given internally in the hope that in their excretion through the lungs they will exercise an antiseptic action in pulmonary disease, but the traces excreted in this way are quite incapable of any noticeable effect on microbial growth and the tubercle bacillus, against which these measures are most frequently directed, appears to be peculiarly resistant to the action of this group of remedies. They are frequently inhaled with a similar object. Some of them have been used as anthelmintics to destroy tapeworm in the intestine, and thymol has recently proved very effective in destroying the intestinal parasites in uncinariasis (see Thymol). Externally some of them are used as mild skin-irritants, generally in the form of spirits. Arnica has a great popular reputation as a stimulating local remedy in bruises and sprains, although it has no specific action and is in no way preferable to the other members of the series.

The volatile oils are important constituents of many of the popular liqueurs, such as Kummel, Maraschino, Curaçoa, Chartreuse, etc., and therefore have a certain dietetic importance.

PREPARATIONS.

Crude Drugs.—Many of the pharmacopœial preparations are whole plants, seeds, leaves or flowers, and are never prescribed, although some of them are used in popular medicine in the form of infusions or "teas." The virtues of these old-fashioned remedies lie perhaps more in the large draughts of warm water than in the traces of volatile oil which they contain, but the presence of the latter prevent, to some extent, the nausea produced by warm water alone. These infusions are used to induce perspiration in fevers or

Bitter almonds → [illegible]

chills, as diuretics, or to relieve colic and griping, and generally contain about a tablespoonful of the herb to one or two cupfuls of water. Those most frequently used for this purpose are peppermint and spearmint leaves and tops (*Mentha Piperita* and *Mentha Viridis,* U. S. P.); Coriander seeds (*Coriandrum,* U. S. P., *Coriandri Fructus,* B. P.); Chamomile flowers (*Anthemis,* U. S. P., and *Matricaria,* U. S. P.); Anise (*Anisum,* U. S. P., the fruit of Pimpinella anisum); Elderflower and Horehound (*Marrubium,* U. S. P., leaves and tops). In different countries, however, the constituents of the herbalist recipes vary according to the local flora. The U. S. Pharmacopœia recognizes a number of other crude drugs of this group, but as these are seldom or never prescribed, they need only be enumerated here: *Rosa Gallica* (red rose petals), *Eucalyptus, Limonis Cortex* (lemon peel), *Aurantii Dulcis Cortex, Aurantii Amari Cortex* (sweet and bitter orange peel), *Caryophyllus* (cloves), *Pimenta* (allspice), *Cinnamomum* (cinnamon), *Sassafras* (sassafras bark), *Cypripedium* (lady's slipper), *Fœniculum* (fennel), *Vanilla* (vanilla), *Cardamomum* (cardamom), *Carum* (caraway), *Myristica* (nutmeg), *Hedeoma* (pennyroyal), *Salvia* (sage), *Sabina* (savine), *Arnica,* and *Zingiber* (ginger). The British Pharmacopœia is less lavishly supplied with these little used crude drugs. It contains, in addition to those first mentioned: *Aurantii Cortex Recens* and *Siccatus* (fresh and dried orange peel), *Cinnamomi Cortex* (cinnamon bark), *Cardamomi Semina* (cardamom seeds), and *Zingiber* (ginger).

Bitter Almonds (Amygdala Amara, U. S. P., B. P.) may be mentioned here, as, although they contain no volatile oil in themselves, one is formed from them when they are bruised in water. They contain a glucoside, amygdalin, and a ferment, emulsin, which, in the presence of water, decomposes the amygdalin into dextrose, prussic acid, and benzaldehyde.

$$\underset{\text{Amygdalin.}}{C_{20}H_{27}NO_{11}} + 3H_2O = \underset{\text{Dextrose.}}{2(C_6H_{12}O_6)} + \underset{\text{Prussic acid.}}{HCN} + \underset{\text{Benzaldehyde}}{C_7H_6O} + H_2O$$

The prussic acid and benzaldehyde, which are probably in combination and not merely mixed together, are known as the oil of bitter almonds, which is much more poisonous than the other volatile oils, owing to its containing prussic acid. Emulsin is also contained in the sweet almond, but no amygdalin, so that no prussic acid is formed when it is pounded in water. The fixed oil of almonds is formed from bitter and sweet almonds, but contains no prussic acid. Laurel leaves, and the bark of the Virginia prune, or cherry (*Prunus Virginiana,* U. S. P., *Pruni Virginianæ Cortex,* B. P.), also contain amygdalin, or some nearly related substance, and emulsin, and form benzaldehyde and prussic acid when rubbed up with water. The Virginian cherry bark has, however, a more bitter taste than the others, from the presence of a resin or some other unknown body.

The **Volatile Oils** themselves are also represented in unnecessarily large numbers in the pharmacopœias.

U. S. P.—*Oleum Menthæ Piperitæ* (oil of peppermint), *Ol. Menthæ Viridis* (spearmint oil), *Ol. Gaultheriæ* (wintergreen), *Ol. Lavandulæ Florum* (oil of lavender), *Ol. Eucalypti* (eucalyptus oil), *Ol. Limonis Corticis* (oil of lemon), *Ol. Aurantii Corticis* (oil of orange peel), *Oleoresina Zingiberis* (ginger), *Ol. Amygdalæ Amaræ* (bitter almonds), *Ol. Caryophylli* (oil of cloves), *Ol. Pimentæ* (oil of allspice), *Ol. Carui* (caraway oil), *Ol. Cinnamomi* (cinnamon), *Ol. Coriandri* (coriander), *Ol. Erigerontis* (erigeron or fleabane), *Ol. Cajuputi* (cajuput), *Ol. Sassafras* (sassafras), *Ol. Anisi* (anise), *Ol. Fœniculi* (fennel), *Ol. Rosmarini* (rosemary), *Ol. Hedeomæ* (pennyroyal), abortifacients *Ol. Juniperi* (juniper), *Ol. Sabinæ* (savine), *Ol. Rosæ* (oil, attar or otto of roses), *Ol. Betulæ Volatile* (volatile oil of birch), *Ol. Thymi* (thyme), *Ol. Myristicæ* (nutmeg).

dose 1-2 drops

B. P.—*Oleum Anethi* (oil of dill), *Ol. Anisi* (anise), *Ol. Cajuputi* (cajuput), *Ol. Carui* (caraway), *Ol. Caryophylli* (cloves), *Ol. Cinnamomi*

Antiseptic action in tooth powders.
Spiritus Menthae Piperitae & of Cinnamomi As Carminatives
As flavors & odors

(cinnamon), *Ol. Coriandri* (coriander), *Ol. Eucalypti* (eucalyptus), *Ol. Lavandulæ* (lavender), *Ol. Limonis* (lemon), *Ol. Menthæ Piperitæ* (peppermint), *Ol. Myristicæ* (nutmeg), *Ol. Rosmarini* (rosemary).

The majority of these oils resemble each other very closely in their effects and require no special comment. Oil of roses is so expensive that it is never used in medicine, especially as it has no special advantages over the others. The oils of rosemary, juniper, and savine are more irritant than the others, and are seldom used. The oils of wintergreen and of birch consist mainly of methyl-salicylate, and may be used instead of the other salicylates. Nutmeg and mace oils are more poisonous than the others, not from their local irritant action so much as from their effects after absorption. Oil of bitter almonds contains a very variable amount of prussic acid and therefore cannot be substituted for the other volatile oils, but its preparations are so dilute as to be void of all danger.

The volatile oils themselves are comparatively little used. A single drop may be added to powders, pills or solutions to give a pleasant odor, and their presence in tooth powders renders these more or less strongly antiseptic. Occasionally they are given in cases of colic or in chill by pouring a few drops on a piece of sugar which is sucked. The dose of the volatile oils in general is 1–2 drops.

Spiritus are formed from many of the volatile oils by dissolving them in alcohol, sometimes with the addition of water and sometimes with some of the crude drugs, so that the preparation is really a mixture of tincture and spirit. The spirits or essences of the volatile oils are used very largely as flavoring agents in mixtures for internal use, and are often added to external applications to lend them odor. They may also be prescribed where alcohol is indicated but is distasteful to the patient; the spirits of the volatile oils contain nearly double the amount of alcohol in brandy, and have to be diluted accordingly. Any of them may be used as carminatives, but the spirits of peppermint, cinnamon, anise and lavender are more frequently used for this purpose than the others. Spirit of juniper is often given as a diuretic, either alone or along with other drugs. Spirit of rosemary is generally used externally. Many of the common perfumes are spirits of different volatile oils; thus eau de Cologne contains the oils of bergamot, lemon, rosemary, lavender and orange-flower, along with acetic ether and alcohol.

The dose of the spiritus as carminatives is 1–4 c.c. (15–60 mins.). They are often prescribed along with other stomachics, such as nux vomica, cinchona, or the bitters.

U. S. P.—*Spiritus Amygdalæ Amaræ, Spir. Anisi, Spir. Aurantii Compositus* (containing the oils of orange peel ,lemon, coriander and anise), *Spir. Cinnamomi, Spir. Gaultheriæ, Spir. Juniperi, Spir. Juniperi Compositus* (containing oils of juniper, caraway and fennel). Dose, 4–8 c.c. (1–2 fl. drs.), *Spir. Lavandulæ, Spir. Menthæ Piperitæ, Spir. Menthæ Viridis.* 4-8cc

Elixir Aromaticum and *Elixir Adjuvans* are preparations of the Spir. Aurantii Compositus, which are used exclusively as flavors.

B. P.—*Spiritus Anisi, Sp. Cajuputi, Sp. Cinnamomi, Sp. Juniperi, Sp. Lavandulæ, Sp. Menthæ Piperitæ, Sp. Myristicæ, Sp. Rosmarini.*

The compound spirit of horseradish (*Spir. Armoraciæ Compositus*) is obtained by extracting the volatile oils of horseradish, bitter-orange peel, and nutmeg with dilute alcohol and purifying them by distillation. Horseradish

Aquae & Syrups as flavoring substances

oil, like that of most of the Cruciferæ, is a sulphur compound, and has a peculiarly hot, burning taste. Dose, 4–8 c.c. (1–2 fl. drs.).

Aquæ.—The volatile oils are very insoluble in water, but when they are shaken in it, enough remains in the water to give it the odor and taste of the oil. In the process of obtaining the oils from the crude drugs by distillation, some oil is held by the water, and a number of these waters (aquæ) are contained in the pharmacopœias. They are used as substitutes for distilled water in making up prescriptions, the small quantity of volatile oil serving merely to give a pleasant odor and taste.

U. S. P.—*Aqua Anisi, Aq. Aurantii Flor.* and *Aq. Aurantii Florum Fortior* (the latter containing twice as much volatile oil as the former), *Aq. Cinnamomi, Aq. Fœniculi, Aq. Menth. Piperitæ, Aq. Menth. Viridis, Aq. Rosæ, Aq. Rosæ Fortior* (the latter twice as strong as the ordinarily used *Aq. Rosæ*).

B. P.—*Aqua Anethi, Aq. Anisi, Aq. Aurantii Florum, Aq. Cinnamomi, Aq. Menthæ Piperitæ, Aq. Rosæ.*

Another preparation containing a volatile oil merely as a flavoring ingredient is *Unguentum Aquæ Rosæ* (cold cream), U. S. P., B. P.

Some of the preparations containing volatile oils are derived not from the oil itself, but from the crude drug, and therefore contain non-volatile substances which are generally absent from the preparations already mentioned. As a general rule these non-volatile bodies are inactive, but in some cases, bitters or resins are contained in the preparations, and may influence their action. Thus a bitter glucoside, hesperidin, is found in the orange peel, and is present in the preparations formed directly from it, while it is absent from those formed from the volatile oil. Ginger contains a resin of hot, burning taste, which increases the carminative action of the oil. Cinnamon contains some tannic acid, which passes over in the tincture, while a fixed oil is contained in cardamom. Arnica contains a bitter substance, arnicin; calamus, a bitter, acorin, in addition to a volatile oil; cascarilla, a bitter principle, cascarillin, along with another oil. Preparations which contain a bitter substance in addition to a volatile oil, are often classed as aromatic bitters along with the Pepper series.

Among the preparations formed from the crude drugs are the **Syrups**, which are used exclusively as flavoring agents.

U. S. P.—*Syrupus Aurantii Florum, Syr. Amygdalæ, Syr. Aurantii, Syr. Rosæ, Syr. Zingiberis, Syr. Pruni Virginianæ.* 2-4 cc

B. P.—*Syrupus Aromaticus* (containing tincture of orange and cinnamon water), *Syr. Aurantii, Syr. Aurantii Floris, Syr. Limonis, Syr. Pruni Virginianæ, Syr. Zingiberis.* Dose of syrups, B. P., 2–4 c.c. (½–1 fl. dr.).

The **Tinctures** are used for the same purposes as the spirits of the pure oils, and in the same dose, 1–4 c.c. (15–60 mins.). The tinctures of arnica are employed externally as applications to bruised surfaces and in similar conditions, but they have no more effect than other preparations, although they are popularly regarded as specifics.

Tinctures
As flavors and carminatives

U. S. P.—*Tinctura Arnicæ, Tinct. Aurantii Amari, Tinct. Aurantii Dulcis,* 1-4 cc *Tinct. Limonis Corticis, Tinct. Cardamomi, Tinct. Cardamomi Composita* (containing cardamom, cinnamon, caraway), *Tinct. Cinnamomi, Tinct. Lavandulæ Composita* (oils of lavender, rosemary, cinnamon, cloves, nutmeg), *Tinct. Vanillæ, Tinct. Zingiberis.*

B. P.—*Tinct. Aurantii, Tinct. Cardamomi Composita* (containing cardamom, caraway, cinnamon and raisins), *Tinct. Cinnamomi, Tinct. Lavandulæ Composita* (lavender, rosemary, cinnamon, nutmeg), *Tinct. Limonis, Tinct. Pruni Virginianæ, Tinct. Zingiberis, Tinct. Cascarillæ.*

Fluid Extracts of the volatile oil series.

U. S. P.—*Fluidextractum Aurantii Amari,* 1–2 c.c. (15–30 mins.).

Fluidextractum Pruni Virginianæ, 2–4 c.c. (½–1 fl. dr.).

Fluidextractum Zingiberis, 0.5–1.3 c.c. (8–20 mins.).

Fluidextractum Aromaticum, 0.5–1.3 c.c. (8–20 mins.), from aromatic powder.

The only fluid extracts at all extensively used are the last three.

Infusions.

U. S. P.—*Infusum Pruni Virginianæ.*

B. P.—*Infusum Aurantii.*

Infusum Aurantii Compositum (formed from bitter orange peel, fresh lemon peel and cloves).

These infusions are given in doses of ½–1 fl. oz. (15–30 c.c.) and may be used instead of the medicated waters (aquæ).

Other Preparations.

Pulvis Aromaticus (U. S. P.) contains cinnamon, cardamom, ginger, and nutmeg in powder, and is a useful carminative in doses of 0.3–2 G. (5–30 grs.).

Pulvis Cinnamomi Compositus (B. P.) contains cinnamon, cardamom and ginger, and is used as a carminative in doses of 10–40 grs.

Pure Principles used as flavors:

Safrolum (U. S. P.), safrol ($C_6H_3 \cdot C_3H_5 \cdot OOCH_2$), a pure principle found in sassafras and other volatile oils, possesses an odor like sassafras. It is a colorless or faintly yellow liquid, soluble in alcohol and ether. Dose, 0.3 c.c. (5 mins.).

Vanillinum (U. S. P.), vanillin ($C_6H_3 \cdot OH \cdot OCH_3 \cdot COH$), occurs in vanilla and is also made synthetically. It forms white needle crystals, slightly soluble in water, easily soluble in alcohol and ether, and possesses the odor and taste of vanilla. Dose, 0.03 G. (½ gr.).

Benzaldehydum (U. S. P.), benzaldehyde (C_6H_5COH), occurs in the oil of bitter almonds, and is also made artificially. It is a colorless fluid with the odor and taste of bitter almond oil, very slightly soluble in water, but freely miscible with alcohol. Dose, 0.03 c.c. (½ min.).

Cinnaldehydum (U. S. P.), cinnamic aldehyde ($C_6H_5CH : CH \cdot COH$), is nearly identical with cinnamon oil and forms a colorless liquid with the odor of cinnamon and a hot, burning taste. Dose, 0.05 c.c. (1 min.).

Eugenol (U. S. P.), a phenol ($C_6H_3OH \cdot OCH_3 \cdot C_3H_5$) obtained from oil of cloves and other oils, and forming a colorless liquid with an odor like cloves, and a hot, burning taste. Dose, 0.2 c.c. (3 mins.).

These principles are used exclusively to give flavor and odor.

A number of other volatile substances are used locally in medicine for the same purpose as the volatile oils, although they are classified in other groups owing to their possessing other properties which are not shared by the oils. Among these may be mentioned especially the preparations of chloroform (aqua, emulsum, spiritus, linimentum), the simple and compound spirits of ether, and acetic ether. These are used largely for the same purposes as the volatile oil preparations, and when administered in moderate quantities do not cause any further effects. The preparations of alcohol known as spirits, or liqueurs, or essences, contain volatile oils—Curaçoa, Cherrywater (Kirchwasser), Kummel, Essence of Mint, etc.—and the simpler spirits, Brandy, Whiskey, Rum, Gin, and the wines contain bodies known as œnanthic ethers, which probably act in a similar way.

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2. Camphor.

Some of the volatile oils deposit crystalline substances or stearoptenes after standing for some time, especially when they are exposed to cold. As a general rule these bodies are present in only small amount, and have not been investigated apart from the volatile oils, of which they form constituents; but a few of them have attracted attention in therapeutics, not only on account of their local effects, which resemble those elicited by the volatile oil group (see page 58), but also because of their action in the tissues after absorption. The chief of these is **Camphor**, which has been used in Chinese medicine for many centuries, and which has also played a considerable rôle in Western therapeutics. It is derived from the Cinnamomum camphora of China and Japan, and possesses the formula $C_{10}H_{16}O$; it is a benzol derivative containing methyl and propyl, in so far resembling the terpenes, from which, however, it differs in the presence of a ketone ($=CO$) link.

Another body closely resembling ordinary camphor is **Borneol** or Borneo-camphor ($C_{10}H_{18}O$), which is derived from the Dryobalanops aromatica, and which apparently differs from ordinary camphor in containing the group ($=CHOH$) instead of ($=CO$). Ngai-camphor, which is obtained from Blumea balsamifera, is very closely related to borneol. Another stearoptene which has been used in medicine apart from the volatile oils, is **Menthol** ($C_{10}H_{20}O$), which is obtained from the oil of peppermint, and apparently contains a CHOH group like borneol, but is more completely hydrated. Borneol

Thujon in absinth causes epilepsy (an isomer of camphor)
Camphor series acts like aromatics, vol. oils & picrotoxin. Skin irritant, hot bitter taste
G.I. warmth, carminative, or vomiting. Absorption = headache. Excitement, pulse slow & skin flushed. Stupor.
2/ epileptiform conv

has been prepared synthetically from camphor, and menthol from menthane, which occurs in oil of peppermint. Thujon, an isomer of camphor occurring in the oil of wormwood or absinth and in many other plants, has not been used in medicine, but is of great importance as the cause of epilepsy in chronic absinthe drinkers.

Several derivatives of camphor which have been examined, resemble it closely in pharmacological action. *Monobromated Camphor* ($C_{10}H_{15}BrO$) has been used in therapeutics, while *Camphorol* ($C_{10}H_{16}O_2$), *Amidocamphor* ($C_{10}H_{15}NH_2O$), *Bornylamine* ($C_8H_{14}(CH_2)(CHNH_2)$) and some other derivatives have been the subjects of experimental investigation.

All of these resemble each other very closely in the effects which they produce in the organism, although they vary in toxicity to some extent. Many of the volatile oils induce the same symptoms, and the camphor group also presents analogies to the simpler bodies of the aromatic series, to which it is so nearly related chemically, and also to picrotoxin.

Symptoms.—Camphor acts as an irritant to the skin and mucous membranes like the volatile oils, and has a hot, bitter taste, and induces in small quantities a feeling of warmth and comfort in the stomach, while after large doses nausea and vomiting may be caused by gastric irritation. It is rapidly absorbed and in large doses induces headache, a feeling of warmth, confusion, and excitement in man, with slowing of the pulse and flushing of the skin. This excitement may be shown in hilarity and delirium with hallucinations, in restlessness, or in sudden violent movements, which pass into epileptiform convulsions. These alternate with pauses of quiet and unconsciousness, which become longer until the patient sinks into complete stupor. In some cases of poisoning no excitement is observed, the patient falling into a condition of drowsiness, unconsciousness and stupor immediately. In the lower mammals, camphor induces very similar symptoms, wild excitement and epileptiform convulsions, followed by depression, stupor, collapse, and death from failure of the respiration. Not infrequently however, the respiration ceases during a convulsion and fails to return when it passes off.

In the frog no excitement is observed except from the local irritation; the animal falls into a condition of depression, in which no spontaneous movements are made, although the reflexes seem to be little affected at first. Later, the reflexes disappear and the animal lies completely paralyzed.

Action: Central Nervous System.—Camphor first depresses the brain in the frog, later the spinal cord, and last of all the terminations of the motor nerves, and the spontaneous movements cease first, therefore, then the reflexes disappear, and finally the muscles fail to contract when the peripheral nerves are stimulated. The cord is capable of conducting impulses from the brain after the reflexes are paralyzed, so that camphor would seem to interrupt the connection between the sensory and the motor cells earlier than that between the motor columns and the cells of the anterior horn (contrast strychnine). Although camphor fails to elicit convulsions in the frog, thujon

First cerebral cortex stimulated (convulsions) then paralyzed.

often induces violent spasms, which appear to arise from stimulation of the spinal cord and medulla oblongata. The exact action of camphor on the spinal cord in mammals is not finally determined, for Stockman found that the reflexes were not increased in mammals by camphor, and he holds that the spinal cord is not primarily stimulated by ordinary camphor, and is in fact depressed by borneol. On the other hand, Gottlieb and Lapin assert that the reflexes are increased by camphor in mammals in which the medulla oblongata has been divided, and that in the bird this increased irritability may even give rise to convulsions. According to them, the spinal cord is finally depressed in mammals by very large doses of camphor, but only after stupor and coma indicate commencing paralysis of the cerebrum.

The convulsions in mammals are certainly not due to any action on the spinal cord, but to stimulation of the higher areas of the nervous axis. The cerebral cortex is involved in the action, for the convulsions are less marked on its removal; but in the lower mammals the chief action seems to be exerted on the nervous centres situated between the cerebral peduncles and the medulla oblongata. It is not improbable that in man the cerebral action may be more marked than that on the lower areas, for on descending lower in the scale it is found that the cerebral action becomes less evident; thus in birds the removal of the cerebrum seems to have no effect on the convulsions. The loss of consciousness and the stupor observed in man and the higher animals point to a final paralysis of the cerebral cortex.

The **Terminations of the Motor Nerves** are paralyzed in the frog by large doses of camphor, but not in mammals. The **Muscles** themselves are weakened and paralyzed when they are directly exposed to its solutions or vapor.

The **Heart** is sometimes slowed by camphor and its allies in man and animals, but is generally little affected in either strength or rate. The frog's heart generally beats more slowly, but the contractions are stronger and fuller according to most observers; these changes arise from action on the muscle fibres, which are rendered more irritable, so that muscarine fails to arrest the frog's heart after camphor, and a heart reduced to inactivity by chloral resumes its rhythmic movements when camphor is applied to it. Gottlieb has stated that camphor lessens the tendency of the mammalian heart to pass into fibrillation under repeated electrical stimulation or spontaneously during experiments; no explanation has been suggested for this action and Winterberg has failed to confirm the observation.

In some mammals the **Blood-pressure** is slightly increased by camphor, in others great variations occur, a very marked rise being observed during the convulsive attacks, while in the interval it falls to below the normal height; these variations indicate that the vasomotor centre is involved in the action of the drug, for they persist when the muscular contractions are eliminated by the injection of

Action on heart, rate & vol. variable. Some direct dil. hence often lower bp. not in convulsions of. Very little circ change unless conv. Ditto resp. In fever an antipyretic. Slight antiseptic. Rubbed into skin = redness & warmth. Menthol at first cold, then heat, then partial anaesthesia. Camphor, menthol etc act same

curara. The peripheral vessels have been found to be dilated by camphor solutions perfused through them, and this action may explain the slight fall in pressure often seen after absorption of the drug.

This slight dilation of the vessels is the only change in the circulation observed after camphor, unless when quantities sufficient to cause convulsions are injected.

The **Respiration** is somewhat slower and deeper than normal, but this alteration is generally insignificant. During the convulsions it is arrested, while in the intervals it may be accelerated from the muscular exertion during the spasms.

The normal **Temperature** is not affected by camphor, but in fever it acts as an antipyretic, like many other aromatic bodies.

Camphor is partially oxidized in the tissues, forming camphorol ($C_{10}H_{16}O_2$), this change perhaps being analogous to that observed in the aromatic hydrocarbons and phenols. It is **Excreted** in the urine in combination with glycuronic acid, as α- and β-camphoglycuronic acid, and also in part in combination with a nitrogenous body, which is probably uramidoglycuronic acid. Camphorol acts like camphor, but its glycuronic acid combinations are inactive, so that the effects of camphor pass off quickly in such animals as the dog, in which these combinations are rapidly formed.

Camphor is possessed of some antiseptic action, although it is much weaker than some of the bodies of the carbolic acid group, and also than many of the volatile oils. Leucocytes cease their movements at once when exposed to camphor solutions or vapor, and Darwin found that it acts as a stimulus to the tentacles of Drosera, an insectivorous plant, and apparently renders them more sensitive to mechanical irritation.

Camphor produces redness and a feeling of warmth when rubbed into the **Skin**. Sometimes, however, a distinct sensation of cold may be experienced, provided the rubbing is not too energetic. Menthol generally induces this feeling of cold, accompanied by more or less prickling, and afterwards by heat and burning. The cold is not due to cooling of the skin, for the vessels of the part are dilated, and the thermometer indicates a higher skin temperature there than in other parts of the body. It has been ascribed to menthol being more irritant to the terminations of certain nerves which convey the sensation of cold than to those of the heat nerves and pain nerves, but this is denied by Rollett who states that menthol acts only on the terminations of the nerves of common sensation or pain. A feeling of numbness and partial anæsthesia follows its application after some time, and a ten per cent. solution has been found to produce anæsthesia of the cornea, which, however, is preceded by pain and smarting.

The action of borneol, menthol, bromated camphor and camphorol is almost identical with that of camphor itself. Borneol is less irritant locally, and the convulsions are less severe than after camphor, so that animals

Tinct camph comp - paregoric 1 fl ʒ = 1/4 gr morph.
Menthol rubbed on
Used to redden over bruises & sprains. Parasiticide ext & int. Carminative. → retards putrefaction as lessens double sulphates.
To prevent chill. Dil. skin vessels to lessen int. congestion

seldom die during the convulsive stage, and may remain in a state of stupor and collapse for one or two days before the respiration finally ceases. After menthol, the convulsions are even less developed than after borneol. Both of these are excreted in combination with glycuronic acid. Bromated camphor seems to resemble borneol more closely than camphor or menthol, while amido-camphor produces symptoms similar to those of camphor, but is much less powerful.

PREPARATIONS.

Camphora (U. S. P., B. P.) ($C_{10}H_{16}O$), Laurel camphor, a stearoptene obtained from Cinnamomum Camphora, forms white translucent, crystalline masses, which are almost insoluble in water but dissolve readily in alcohol, ether, chloroform, fixed and volatile oils. 0.1–0.6 G. (2–10 grs.), in emulsion or pill. 2-10 gr

✓ *Aqua Camphoræ* (U. S. P., B. P.).

✓ SPIRITUS CAMPHORÆ (U. S. P., B. P.), 0.3–2 c.c. (5–30 mins.). 10%

LINIMENTUM CAMPHORÆ, camphorated oil (U. S. P., B. P.). 20%

TINCTURA CAMPHORÆ COMPOSITA (B. P.), paregoric, contains 1 part of morphine in 2000, *i. e.*, each fluid drachm is equivalent to ¼ grain of opium. ½–1 fl. dr.

Linimentum Camphoræ Ammoniatum (B. P.), compound camphor liniment.

Camphor is also an ingredient in the camphorated tincture of opium, or paregoric (U. S. P.) and in soap liniment and chloroform liniment.

Camphora Monobromata (U. S. P.), monobromated camphor ($C_{10}H_{15}BrO$), consists of colorless crystals which are insoluble in water, soluble in alcohol and ether. 0.3–1 G. (5–15 grs.), in emulsion or pills.

Menthol (U. S. P., B. P.) ($C_{10}H_{20}O$), a stearoptene obtained from the official oil of peppermint or from Japanese or Chinese oil of peppermint, consists of colorless crystals slightly soluble in water, freely soluble in alcohol or ether. It is used externally in alcoholic solution or moulded into sticks and pencils, which are rubbed on the affected part.

Borneol or Borneo camphor ($C_{10}H_{18}O$), a stearoptene obtained from Dryobalanops Camphora, resembles camphor in appearance and solubility, but has not been used in therapeutics and is not official.

Therapeutic Uses.—Camphor is used externally in the form of the liniment or spirit as a mild rubefacient in bruises and sprains, and also to destroy parasites. Internally the spirit is prescribed as a carminative and as an intestinal disinfectant. Its administration for the latter purpose has been shown to be followed by a diminution of the double sulphates of the urine, so that it seems to retard the putrefaction in the bowel to some extent. The spirit is frequently given to prevent "chill," and may relieve the congestion of internal organs through dilating the skin vessels.

It was formerly administered in cases of abnormal irritability of the central nervous system, such as epilepsy and various other forms of convulsions, including those produced by strychnine, but its action would seem to contraindicate its use here and camphor is scarcely prescribed in these cases now.

It has been used, apparently with success, as a stimulant to the central nervous system in unconsciousness and collapse arising from different causes, and in the depression and weakness of acute fevers. In many of these cases, a marked improvement in the pulse has been observed after camphor; this, like the similar improvement seen

us. stim. in collapse [illegible] [illegible] from fevers.
[illegible] due to reflex action. Swelling when by hypo + as insol in water
slowly absorbed so action slow to NS. With opium as expectorant

Eliminated by kidney combined by glycuronic acid.

Menthol depresses sensory endings in headache + neuralgia

after alcohol, may perhaps be explained by its action as a local stomachic irritant producing changes in the circulation reflexly. Solutions of camphor have been injected subcutaneously in these cases, but they cause pain and swelling at the point of injection. Camphor is almost entirely insoluble in watery fluids and is apparently absorbed slowly and with difficulty in some conditions, and this may explain the absence of effect in many cases of collapse treated with it.

Camphor is often prescribed in expectorant mixtures, especially in combination with opium, as in paregoric.

It has been advised in hysteria, and both as an aphrodisiac and as an anaphrodisiac. Any effect in these conditions must probably be ascribed rather to hypnotic suggestion than to the real action of the drug.

Menthol is used almost exclusively for its effects on the sensory nerve treminations, and is applied by rubbing the crystals or sticks on the skin in case of headache and neuralgia.

Borneol and monobromated camphor are entirely superfluous. The latter was at one time used as a sedative in nervous excitement, but does not seem to have been at all beneficial and has fallen into disuse.

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Musk is the dried secretion of the preputial follicles of Moschus moschiferus, the musk deer of Thibet. It forms a dark, reddish-brown, crumbling mass, with a very strong characteristic odor. About 10 per cent. is soluble in alcohol, about 50 per cent. in water.

Musk has long been reputed to have a very powerful action in collapse and hysteria, but is rarely procurable at the present day, except in a very much adulterated form. Very little is known with certainty as to its composition, and the odoriferous matter, which is believed to be the active principle, has scarcely been examined.

Earlier investigators describe various indefinite subjective symptoms, drowsiness and sleep from the use of musk, but Hermans, who studied the subject more recently, could find no effects from the administration of musk to men or animals. It is rarely used at the present time, and may be considered entirely superfluous.

Piperine (black pepper) insol H2O. All are carminatives. Capsicum Ginger, Syrup G. flavor + carminative. Tinct. Capsici (1cc) for chronic alcoholism — irritant on stomach.

3. Pepper Group.

Several drugs which act as carminatives like the volatile oils, but which differ from them in the nature of their active constituents, may be mentioned here.

Black Pepper contains a weakly basic substance, *Piperine* (which is broken up by caustic alkalies into *Piperidine* and *Piperinic acid*), in addition to a volatile oil and a bitter pungent resin. According to Buchheim a second base, *Chavicine,* also exists in it and can be decomposed into *Piperidine* and *Chavicic acid.* Piperine is insoluble in water, and has therefore no taste when absolutely pure, but is hot and pungent to the taste when it is taken in solution.

Pyrethrum, or pellitory, contains similar constituents, volatile oil, resin and *Pyrethrine,* which is decomposed into *Piperidine* and *Pyrethric acid* (Buchheim).

The unstable alkaloid, *Sedine,* of Sedum acre (biting stonecrop), resembles the pepper alkaloids in its effects, but has not been accurately examined as yet.

Capsicum, or Cayenne pepper, contains a number of ill-defined, non-volatile bodies, which have been termed *Capsicol, Capsaicin, Capsicin,* etc., but of which little or nothing is known accurately. As it has no volatile oil, it differs entirely from the other members of the series, but it acts similarly in the stomach, and is used frequently as an irritating carminative.

Ginger might also be included here, as it owes its pungency in part to the presence of a resin along with the volatile oil.

The volatile oils derived from the Cruciferæ differ from the others in containing sulphur, and in possessing a much more irritating action. Thus the volatile oil of mustard might be treated of along with the peppers rather than with the other volatile carminatives, but mustard is used in medicine only as a skin irritant, and will be taken up in that connection (see page 91). The horseradish (Armoracia, B. P.) and the formerly official scurvy-grass (Cochlearia officinalis) are used as carminatives, and owe their activity to their containing similar or identical sulphur compounds.

These drugs differ from the volatile oils only in being more irritant when applied to the skin and alimentary canal. The absorption of large quantities has led to inflammation of the kidney in some instances.

Pepper and capsicum are largely used as condiments, and are comparatively seldom prescribed in therapeutics. Both are used in domestic medicine as skin irritants, and capsicum is prescribed where a strong stomachic irritant is required. The tincture has been employed in chronic alcoholism in order to provide a substitute for the local irritant effects of spirits in the stomach. Ginger preparations are added to other remedies as flavoring agents, the syrup being generally used, and they are also among the best of the carminatives. The lozenges are prescribed in chronic inflammatory conditions of the pharynx and larynx. Pyrethrum is rarely employed. Piperine has been advised in malaria as a substitute for, or adjuvant to quinine, but has fallen into disuse. Pepper has been administered internally as a genitourinary disinfectant and stimulant.

PREPARATIONS.

Piper (U. S. P.), black pepper, the unripe fruit of Piper Nigrum.
Oleoresina Piperis (U. S. P.), 0.03 G. (½ gr.).
Piperinum (U. S. P.), 0.1–0.5 G. (2–3 grs.).
Pyrethrum (U. S. P.), pellitory, the root of Anacyclus Pyrethrum.
Tinctura Pyrethri (U. S. P.).
Zingiber (U. S. P., B. P.), ginger, the rhizome of Zingiber officinale. U. 8 cc
Syrupus Zingiberis (U. S. P., B. P.), 4–8 c.c. (1–2 fl. drs.).

Tinctura Zingiberis (U. S. P., B. P.), 2–4 c.c. (½–1 fl. dr.).
Fluidextractum Zingiberis (U. S. P.), 0.5–1 c.c. (5–15 mins.).
Oleoresina Zingiberis (U. S. P.), 0.03 G. (½ gr.).

Capsicum, Cayenne pepper, chillies, the fruit of Capsicum fastigiatum (U. S. P.); **Capsici Fructus,** the dried fruit of Capsicum minimum (B. P.).

1 cc – *Tinctura Capsici* (U. S. P., B. P.), 1 c.c. (15 mins.).
Oleoresina Capsici (U. S. P.), 0.03 G. (½ gr.).
Fluidextractum Capsici (U. S. P.), 0.03–0.1 c.c. (½–2 mins.).
Emplastrum Capsici (U. S. P.).
Unguentum Capsici (B. P.).

Armoraciæ Radix (B. P.), horseradish root, the fresh root of Cochlearia Armoracia.

Spiritus Armoraciæ Compositus (B. P.), 1–2 fl. drs. (See p. 66.)

Piper Methisticum, or Kava Kava, is used in the South Sea Islands to prepare an intoxicating liquor, which according to Kesteven, differs from the alcoholic preparations in producing marked muscular weakness without affecting the mental powers. Other observers state, however, that it causes confusion and sleep very much as alcohol does. Its local action resembles that of pepper, and like it, it has been advised in gonorrhœa. Its virtues seem to reside in two resinous bodies.

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4. Malodorous Volatile Oils.

Some of the volatile oils differ from the others in possessing an odor which is disagreeable and nauseating to most people, although not to all. The best known of these are the *Oils of Asafœtida* and *Valerian.* The former occurs along with resins and gums exuding from some species of Ferula, and contains several organic sulphur compounds, to which it owes its odor. Oil of Valerian,[1] from Valeriana officinalis, is almost without odor when freshly distilled, but when kept for some time and exposed to the air, it assumes a somewhat unpleasant, penetrating odor. It contains two terpenes, borneo-camphor, and numerous esters of formic, acetic and valerianic acid. While both of these oils are generally regarded as possessing very unpleasant odors, asafœtida is used in India as a condiment, and valerian was formerly used in England as a perfume. Another species of Ferula which is included in the pharmacopœias, but of which little is known, is *Sumbul,* the root of Ferula Sumbul. It has a strong musk-like odor, and is sometimes used to adulterate musk.

Asafœtida and valerian are used in hysterical affections, and the benefits accruing from their administration have generally been attributed to the mental impression produced by their unpleasant odor and taste, and not to any action they produce after absorption.

But Kionka[2] states that valerian, in small doses, has a definite

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[1] *Sikorska,* Thèse de Geneve, 1899.
[2] Arch. Internat. de Pharmacodyn., xiii., p. 215.

For hysteria – disagreeable odor & taste.
Carminatives, expectorants.
G.U. Disinfectants – Copaiba, cubebs, sandalwood

stimulating action on the psychical functions and the circulation, and that this is due to the presence of certain valerianic esters in the oil. Some artificial compounds (*Valyl*) possessing similar properties have also been formed. The ordinary valerianic salts have no further effects than other salts of the acetic acid series, so that it is quite irrational to use such bodies as valerianate of quinine for their action in hysteria.

Asafœtida is also used like the other volatile oils as a carminative and as an expectorant, and the emulsion is given by the mouth or in an enema to relieve abdominal distention.

Preparations.

Asafœtida (U. S. P.), a mixture of volatile oil, gum, and resin from Ferula fœtida.

Emulsum Asafœtidæ, 15–30 c.c. (½–1 fl. oz.). 15–30 cc

Pilulæ Asafœtidæ, 1–3 pills.

Tinctura Asafœtidæ, 1–2 c.c. (15–30 mins.).

Asafetida (B. P.), a gum-resin obtained from the root of Ferula fœtida and probably other species.

Tinctura Asafetidæ, ½–1 fl. dr.

Pilula Aloes et Asafetidæ, 4–8 grs.

Pilula Galbani Composita, 4–8 grs.

Spiritus Ammoniæ Fetidus, 20–40 mins. for repeated administration; for a single administration 60–90 mins.

Valeriana (U. S. P.), **Valerianæ Radix** (B. P.), valerian, the rhizome and roots of Valeriana officinalis.

Fluidextractum Valerianæ (U. S. P.), 2–4 c.c. (½–1 fl. dr.).

Tinctura Valerianæ (U. S. P.), 4 c.c. (1 fl. dr.). 4 cc

Tinctura Valerianæ Ammoniata (U. S. P., B. P.), 1–4 c.c. (15–60 mins.).

5. Volatile Oils Used as Genito-urinary Disinfectants.

Another group of volatile oils is used chiefly for genito-urinary disinfection. The best known of these are the *Oils of Copaiba, Cubebs and Sandalwood,* which resemble each other closely in character. Oil of cubebs and oil of copaiba contain a large proportion of sesquiterpene ($C_{15}H_{24}$), and the oil of sandalwood has two oxidized substances (santolol and santalal), which can be reduced to a sesquiterpene identical with that of copaiba. In copaiba the volatile oil is associated with one or more resinous acids, and in cubebs there is in addition to resinous acids a bitter substance, *Cubebin,* which is not absorbed from the stomach and bowel, however, and is entirely inactive. Cubebs and copaiba have long been used as genito-urinary disinfectants, while sandalwood oil is a more recent addition to the group, which is less disagreeable to take and has less tendency to disturb the digestion.[1] The oils have the ordinary effects on the skin, stomach and intestine, are absorbed, and are excreted partly by the lungs, but chiefly by the

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[1] The ideal genito-urinary disinfectant of this series ought to be well borne by the stomach and bowel, and ought to be excreted mainly by the kidneys in a fairly strong combination with glycuronic acid, as, if the latter is easily split off in the urine, it is liable to act as a culture medium for bacteria. (Schmiedeberg.)

Out in urine as glucuronates etc. Fehlings; ferments slowly. Lessen exudate in gonorrhoea. Used in chronic cases

kidneys in combination with glycuronic acid; some oil is unchanged, some is partially oxidized in the tissues.

The products of the oils excreted in the urine appear to have some antiseptic action, for the urine of persons treated with them putrefies more slowly than ordinary urine and the growth of many of the more common germs is somewhat retarded by it. On the other hand there seems some question as to how far it is destructive to the gonococcus, which sometimes grows readily in culture media made up with such urine instead of water. Winternitz therefore attributes the undoubted therapeutic efficacy of these oils to their lessening the inflammatory exudate rather than to their antiseptic action, without denying that the latter may also be of some importance. In large quantities, these oils cause irritation in the bladder and urethra, which leads to a constant desire to micturate, and to much pain and difficulty in doing so; sometimes the pain is so great as to lead to complete retention. When the urethra or bladder is in a state of inflammation, these symptoms are produced by even small doses, so that these oils are generally avoided in the acute stages of inflammation, and only given later when the disease has passed into the subacute or chronic stage. They are used in some inflammatory affections of the bladder, but much more extensively in gonorrhœa.

Copaiba and cubebs both contain resinous acids in addition to the volatile oil, and these possess considerable diuretic powers, and are also credited, along with the oils, with some action on the bronchial mucous membrane, so that they often form constituents of "expectorant" mixtures, prescribed to lessen the secretion of the bronchi. These resins are excreted in the urine, and are precipitated by the addition of acids; when the nitric acid tests for albumin are employed after copaiba, a precipitate is accordingly obtained, and may be mistaken for albumin, but can easily be distinguished from it by the addition of alcohol, which redissolves the resin but not the protein. The urine is often found to reduce Fehling's solution, in some cases apparently from the presence of sugar, in others from the glycuronic acid combined with the oil. The oil of sandalwood is excreted more rapidly than the others. Copaiba and cubebs are less irritant to the stomach than many of the other volatile oils, but after their prolonged administration (especially in the case of copaiba) symptoms of gastric disturbance sometimes appear in loss of appetite and uneasiness in the stomach. Sandalwood oil is said to be less irritant than the others. Occasionally skin eruptions occur after the use of these oils; they are generally of the nature of urticaria, sometimes of erythema nodosum, and only very rarely is eczema seen. The cause of these skin eruptions is unknown, but they may be due to the gastric disturbance.

PREPARATIONS.

Copaiba (U. S. P., B. P.), Balsam of Copaiba, Copaiva, the oleoresin of Copaiba Langsdorffii and of other species of Copaifera. Dose, 0.5–1.3 c.c. (10–20 mins.); B. P., ½–1 fl. dr.

Oils in capsules, acacia-emulsions

Oleum Copaibæ (U. S. P., B. P.), the oil freed from the resin by distillation, 0.5–1 c.c. (10–15 mins.). 1/2 - 1 cc

Cubeba (U. S. P.), **Cubebæ Fructus** (B. P.), Cubebs, the unripe fruit of Piper Cubeba.

Fluidextractum Cubebæ (U. S. P.), 0.5–2 c.c. (10–30 mins.).
Oleoresina Cubebæ (U. S. P.), 0.5 G. (7½ grs.).
Tinctura Cubebæ (B. P.), 4–8 c.c. (1–2 fl. drs.).
Oleum Cubebæ (U. S. P., B. P.), 0.5–1 c.c. (10–15 mins.). 1/2 - 1 cc
Trochisci Cubebæ (U. S. P.).

Oleum Santali (U. S. P., B. P.), Sandalwood oil, distilled from the wood of Santalum album. Dose, 0.5–1 c.c. (10–15 mins.). 1/2 - 1 cc

Therapeutic Uses.—As has been mentioned, these drugs find their most extensive application in the subacute stages of cystitis and gonorrhœa.[1] They are also used in bronchial disease with an excessive flow of mucopurulent secretion; less often copaiba is prescribed along with other diuretics to promote the secretion of urine. The cubeb lozenges are sucked in hoarseness and relaxed sore throat, and often give relief owing to the pungent stimulating action.

In gonorrhœa the therapeutic agent is undoubtedly the volatile oil, the resin having little or no antiseptic action. The oils and the oleoresins are often administered in capsules, as they have an unpleasant odor and taste, especially those of copaiba. They may also be given as emulsions, and cubebs is sometimes prescribed as a powder suspended in mucilage.

Several other oils have been used as substitutes for Copaiba and Cubebs. Among these may be mentioned Gurjun Balsam, which is obtained from Dipterocarpus alatus, and contains a sesquiterpene and a resin. It has been used in gonorrhœa and as a local application in leprosy.

Matico, the dried tops of Piper angustifolium, which contains a volatile oil, resin and acid, has also been used in gonorrhœa to some extent.

Its pharmacopœial preparation is
Fluidextractum Matico (U. S. P.), 1–3 c.c. (15–45 mins.).

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Sachs. Wiener. klin. Woch., xv., p. 442.
See also the bibliography of the volatile oils in general.

6. Uva Ursi (Arbutin).

A number of drugs which are used for almost the same purposes as the cubebs series, but which do not all owe their activity to volatile oils, may be mentioned here.

Uva Ursi.—The leaves of the bearberry, Arctostaphylos Uva-Ursi, and of allied plants contain two glucosides, *Arbutin* and *Methylarbutin*, along with large quantities of tannin, an inactive glucoside, *Ericolin*, and a neutral insoluble body, *Urson*. These glucosides are decomposed by the action of acids or of emulsin into glucose and hydroquinone or methylhydroquinone, bodies of the benzol series. A part of the arbutin administrated in therapeutics seems to undergo this decomposition in the body, but most of it is eliminated by the kidneys unchanged. It is possible that the small quantity of hydroquinone and methylhydroquinone which appears in the urine is formed from arbutin by the bacteria of the intestine, and not by the activity of the tissues.

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[1] Other remedies which have some reputation in these conditions are urotropin and the salicylic compounds.

Uva ursi is found to have some diuretic action, which is obviously due to its acting on the renal epithelium, and the urine is found to undergo putrefaction much more slowly than usual. This was at one time believed to be due to the formation of hydroquinone, but it seems more likely that arbutin itself is a slight stimulant to the renal cells, and that it is also weakly antiseptic. It is still undecided how far the other constituents of uva ursi are active, but there is little doubt that the arbutin and methylarbutin are the chief principles.

The urine is often dark in color after uva ursi or arbutin, and this tint deepens when it is allowed to stand and undergo putrefaction. The coloration is due to the hydroquinone, which is subject to further oxidation, and forms brownish-green pigments similar to those seen in the urine after carbolic acid and its allies. When decomposition of the urine occurs in the bladder, as in cystitis, the urine may have this dark color when passed. In these cases probably less of the arbutin escapes undecomposed, but this has not been demonstrated.

Large quantities of uva ursi cause nausea, vomiting and diarrhœa, but Lewin states that this disturbance of the alimentary canal may be avoided by filtering the watery preparations through animal charcoal, or by administering the glucosides instead of the cruder preparations.

Buchu, the leaves of several species of Barosma, contain a volatile oil, one constituent of which is a camphor body, *Diosphenol*. This volatile oil is absorbed and is excreted by the kidneys, and renders the urine slightly antiseptic. It does not increase the renal activity appreciably.

Zea, or cornsilk, contains a resinous acid which increases the secretion of urine by direct stimulation of the renal epithelium.

Chimaphila, or pipsissewa, contains a volatile substance, *Chimaphilin*, and arbutin, and is used as a substitute for Uva ursi.

PREPARATIONS.

Uva Ursi (U. S. P.), **Uvæ Ursi Folia** (B. P.), the leaves of Arctostaphylos Uva-ursi (bearberry).

Fluidextractum Uvæ Ursi (U. S. P.), 5–15 c.c. (1–4 fl. drs.).

Infusum Uvæ Ursi (B. P.), ½–1 fl. oz.

Buchu (U. S. P.), **Buchu Folia** (B. P.), the leaves of Barosma betulina and B. crenulata.

Fluidextractum Buchu (U. S. P.), 2–4 c.c. (30–60 mins.).

Tinctura Buchu (B. P.), ½–1 fl. dr.

Infusum Buchu (B. P.), 1–2 fl. oz.

Arbutin has been advised as an improvement on the crude Uva ursi. It is given in doses of 1–4 G., in sweetened solution.

Therapeutic Uses.—These drugs are all used as mild disinfectants of the urinary tract, and are generally prescribed along with more powerful diuretics. They are said to give relief in catarrh and inflammation of the bladder, but are of little importance.

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Paschkis. Wiener Med. Presse, 1884, p. 398.
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Rubefacient, reddening warmth, tingling, blister, pustule, abscess, rise in art. pressure - active heat & constriction of splanchnic arterioles - extra supply to skin & muscles, slowed breathing, increased metabolism increased consciousness, lowered int. temp., higher art.

VI. SKIN IRRITANTS AND COUNTER-IRRITATION.

The practice of applying irritants to the skin in internal diseases is one of great antiquity. The theories on which this therapeutic method is based have changed with the advance of medical knowledge, until, no explanation satisfactory to modern scepticism being forthcoming, the use of these remedies has fallen into a certain disrepute in the last few years. The old theory of revulsion or derivation was at first based on the belief that disease was a malignant entity or humor, which might be drawn from the deeper organs to the surface by means of irritation of the skin. Later, it was supposed that the congestion of the diseased organs might be relieved by the withdrawal of fluid to the skin, and this belief has been held in more or less modified forms in quite modern times. In addition, it was recognized very early that irritation of the skin relieved pain in many instances. The means by which the skin irritation was attained were extremely numerous and varied; large numbers of drugs have been used, and in addition mechanical devices of all kinds were employed, such as burning, electrical currents, or the introduction of setons. In many of these the idea of irritation was combined with that of leaving a way of escape for humors. This latter is only of historical interest, but the practice of relieving internal organs by external irritation or *counter-irritation* persists still, and perhaps merits more attention than it receives at the hands of many physicians.

The effects of an irritant applied to the skin are local and remote. The first symptoms of irritation are congestion and redness of the part, and many drugs which produce only this degree of irritation in ordinary circumstances, are known as *Rubefacients.* Stronger irritants cause blistering, and are called *Vesicants,* while some drugs which cause irritation and small ~~discrete suppurati~~ons, receive the name of *Pustulants.*

Local Symptoms.—The application of an irritant to the skin causes a feeling of warmth, and often of itching, which may later become intensified into actual pain. The skin becomes red, congested, warm, and at first is more sensitive to touch and painful stimuli, though the sensitiveness is afterwards lessened. This condition persists for a longer or shorter time according to the nature of the irritant, and then passes off slowly. Very often desquamation follows, if the rubefacient has acted for some length of time. Stronger irritation is followed at first by the same results, but soon small globules of fluid appear below the epidermis, and these coalesce so as to form a large accumulation of fluid, which raises the epidermis completely off the true skin, forming a blister. If the irritant be removed, the fluid of the blister undergoes a slow absorption, so that in the course of a few days the epidermis forms an empty sack, which, however, is not obliterated by the adhesion of the walls. If the blister be opened,

Pustulants irritate + close orifices of skin glands → pus
Hyperaemia due to dilatation in vessels not to reflex. Dil of vessels
& slowing of current = transudation of fluid + w.b.c. ~~+ irritant~~ = blister
+ irritant = inflammation

the sensitive dermis is exposed, and the secretion of fluid continues for some time, until a new epidermis has been formed.

The distinct and separate points of inflammation caused by the pustulants are due to their affecting the orifices of the skin glands and not intervening tissue. This has been ascribed in some instances to the drug being rendered irritant at these points by the presence of acids formed by the decomposition of the sebum and perspiration; a simpler explanation is that the pustulants cannot pass through the horny epidermis, but act as irritants wherever they come in contact with living tissue, that is, at the orifices of the glands. They cause the same sensation of warmth and prickling of the skin as the other irritants, but even in the earlier stages of their action small, dark-red, raised points are observed, exactly as in some of the exanthemata, and these afterwards form small abscesses. If the application be persisted in, these discrete abscesses may burst through the intervening tissues and become confluent, and large abscesses have thus been formed in the skin. When the irritant is removed before the formation of pus, the inflammation of the ducts slowly subsides and the epidermis peels off as after the milder irritants. Pustulants are seldom employed at the present time; croton oil applied vigorously may induce pustulation, and tartar emetic was formerly largely used for this purpose.

The local effects of the rubefacients and vesicants are identical with those of acute inflammation. The pain and discomfort are due to the action on the nerve terminations, while the redness and swelling betray the local dilation of the vessels. This latter is perhaps due to the direct effect of the irritant on the vessel walls, rather than to any reflex action from the irritation of the sensory nerves, but it cannot be said to be known how far this agency is involved in the result. The dilatation of the vessels and the slowing of the blood current in them lead to the transudation of fluid and leucocytes into the tissues, especially at the points where the irritation is greatest, and the accumulation eventually pushes off the horny epidermal layer from the living layers and forms a blister. The fluid in the blister has been shown to contain some of the irritant, which diffuses into it through the epidermis. The œdema and swelling is not confined to the skin, but extends into the subcutaneous tissue and the more superficial layers of muscle.

If the irritation be continued long enough, suppuration may commence in the blister and lead to deep erosion of the tissues.

Remote Action.—Local irritation cannot exist without causing certain general changes which affect the whole organism. These arise from the reflex stimulation of various centres in the medulla oblongata, and are thought to explain many of the beneficial effects of counter-irritation. Attempts to base the explanation of counter-irritation on these general effects have all failed, however, and many of them are elicited only by widespread irritation or by more intense localised irritation than is induced by ordinary therapeutic methods.

Reflex on centers in medulla - heart, vessel tone, resp. Constriction of splanchnics = vaso to skin & extremities. Alteration in int & ext. temp. Leucocytosis

The centres involved are those regulating the heart, the tone of the vessels, and the respiration. Moderate irritation of the skin causes an acceleration of the heart-rhythm, which has not been satisfactorily explained, while more powerful irritation slows the heart through the inhibitory centre. The blood-pressure measured in the arteries is considerably increased by ordinary irritation of the skin, but if it be very severe or widespread, the slowness of the pulse may cause a fall of tension. This increase in the blood-pressure is due to the reflex stimulation of the vasomotor centre, which causes a constriction of the arterioles over wide areas of the body. The constriction is not general, however, but seems to affect the abdominal organs chiefly, while the vessels of the limbs and probably those of the skin are not contracted. The result is that while the blood-pressure is raised equally throughout the body, the resistance to the circulation is greater in the abdominal organs than in the rest of the body, and more blood is accordingly supplied to the muscles and skin and less to the internal organs than normally.

The effects of skin irritation on the respiration are less uniform. In the rabbit the breathing is sometimes accelerated, sometimes slowed by mild stimulation, while stronger stimuli seems to slow it always. The effect of the application of skin irritants on the respiration in man has not been observed accurately, but that sudden stimulation of the skin causes gasping and irregularity of the respiration, may be observed whenever cold water comes in contact with the more sensitive parts of the body.

The temperature of the body also undergoes changes when the skin is irritated. When the irritation is slight, an increase in the rectal temperature is often observed at first, while a decrease follows later, but on powerful stimulation, the preliminary rise of temperature is so short as to escape observation by ordinary methods, while the subsequent fall is more distinct and prolonged. The skin temperature is raised at the same time as the internal temperature falls. The explanation of these changes in the internal and external temperatures is obviously the altered distribution of the blood, more of which flows through the skin vessels and is cooled than usual. This results in a fall of the internal temperature and a rise in that of the skin, through the warm blood from the interior of the body pouring through the superficial vessels. The preliminary rise in the temperature has not been explained. The whole subject of the alteration of the temperature through counter-irritation has perhaps received greater attention than it deserves, if the observations of Jacobson be correct, for he found the variations in man to amount to less than one-tenth of a degree Centigrade as a general rule.

The metabolism has been found to be altered by the application of irritants to the skin, and, although in the experiments on which this statement is based, the surface exposed to the irritant was larger than that affected in therapeutics, it seems probable that some change is produced by the ordinary agents also. Zuntz and Röhrig found that bathing animals in strong salt solution increased the oxygen absorbed and the carbonic acid excreted much more than bathing in ordinary water, and Paalzow obtained the same result from the application of mustard plaster. The nitrogen of the urine is also said to be increased. This increase in the oxidation of the tissues is of the same nature as that produced by cold, and is due to an augmentation of the muscular activity, which, however, is too slight to cause any perceptible movement.

Irritation of the skin induces leucocytosis in the same way as irritation of the alimentary canal. This is especially evident after the application of a vesicant such as cantharides plaster, while rubefaction seems to have less effect. The injection of irritants into the subcutaneous tissues induces a leucocytosis similar to that following cantharides.

Lastly, in considering the effects of skin irritation on the general vitality, it may be mentioned that a sudden application may awake the consciousness, as is seen in the effects of dashing cold water on the chest, or of striking the hands in narcotic poisoning. Another example is seen in the improved mental condition so often observed in fever patients treated with cold baths. This improvement is due to the changes in the skin, and not, as is often said, to the fall in temperature, for the latter is often insignificant.

FIG. 1.

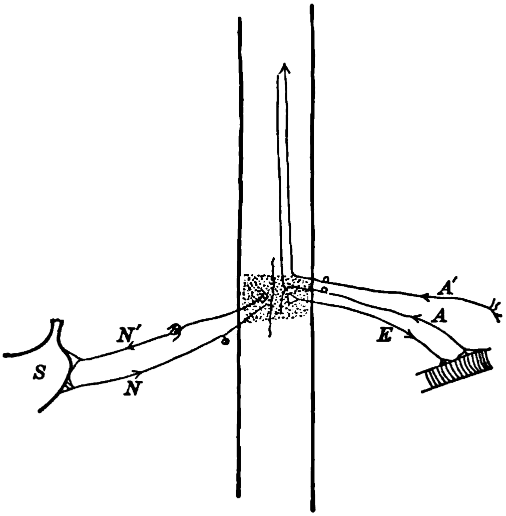


Diagram to illustrate the effects of visceral disease on sensation (after Mackenzie). *S*, diseased viscus, with afferent nerve fibre *N* and efferent fibre *N'* arising from the same area of the spinal cord. The impulses from the diseased area induce a condition of heightened sensibility in the shaded area. *E*, a motor nerve fibre to muscle, which carries more impulses than usual from the area in the cord and thus leads to a tonic contraction of the muscle. *A*, the afferent nerve from the muscle and *A'* from the skin entering the cord in the sensitive area and thus giving rise to the sense of pain and tenderness.

All of these effects are produced by irritation at any point of the surface, and are quite insufficient to explain the practical use of counter-irritants to affect a particular organ. For example, in gastric disorders a counter-irritant is often applied just over the ensiform cartilage, while in facial neuralgia a blister behind the ear often gives relief. If the beneficial results were due to the general alteration of the circulation, respiration, or temperature, there would be no reason to vary the point of application, for the effect would not vary. Zuelzer, therefore, attempted to ascertain whether the deeper tissues and the internal organs were affected by superficial irritation over them, and found that when cantharides was applied to one side of a rabbit's back for fourteen days, the superficial muscles under it were congested, while the deeper layers and the lung were anæmic when compared with the corresponding parts on the other side. His treatment, however, led to necrosis and suppuration, so that his conclusions are not unimpeachable. Lazarus-Barlow and Philipps observed recently that the muscles on the same side

Counterirritation - dil vessels of organ beneath corresponding skin
area. Stimulates normal impulses to + from skin & thereby
overshadows referred pain from organ to cord segment to skin

as, but at some distance from a blister, were of higher specific gravity than those on the uninjured side, while those immediately below the blister were of lower specific gravity, and therefore concluded that fluid was drawn from the deeper muscles to supply the superficial ones. This, however, evidently requires that the internal organs to be affected must be not only contiguous, but also continuous with those directly affected, and offers no explanation of the alleged effects of irritation of the skin upon the stomach or lungs.

Much light has been thrown on the subject by the observations of Mackenzie and Head, who found that visceral disease is often accompanied by tenderness of the skin and underlying muscles, and that the pain arising in these cases is referred to this area of skin and not to the organ involved. Thus in painful diseases of the stomach, tenderness is often found in the skin and muscles of the epigastrium, while in œsophageal stricture, pain may be referred to a point near the angle of the scapula and to another in the neighborhood of the apex-beat. Similarly in heart disease, pain is often felt in the left chest-wall and shoulder extending down the left arm. These points are, of course, only connected with the diseased organ by means of nerve-fibres, and it thus appears that impulses from such an organ arouse a condition of heightened sensibility in the region of the cord on which they impinge; this affects all the synapses in the neighborhood (Fig. 1), so that impulses from very different structures may be altered by the affection of one. The sensation of pain aroused by this exaggerated sensibility is of course referred to the periphery, not to the focus in the cord, and this gives the impression of tenderness in the skin and muscles. It therefore seems probable enough that an affection of these superficial areas may affect the corresponding internal organ more than the rest of the body, and this is exactly what is required to explain the benefits derived from the use of counter-irritants. It is especially noticeable that several of the points affected by internal disease are precisely those points at which experience has shown irritation to be most beneficial (Fig. 2). Thus the application of a blister over the epigastrium has long been recognized as a means of relieving gastric disorders. Similarly the old treatment of iritis by means of a blister on the temple may be justified by the fact that Head found areas of tenderness on the temple accompanying this disease.

The exact nature of the effects of counter-irritation on the internal organs has not been ascertained, but it would seem most probable that an alteration in the calibre of the vessels is induced. These alterations may be accompanied by changes in the activity of the organs; for example, there seems good reason to believe that in many cases irritants applied to the abdomen produce evacuation of the bowels. The most obvious effect of counter-irritation very often is the relief of pain, and this seems explicable in the light of the observations of Mackenzie and Head. For if the pain in visceral disease is due to the disorder of the synapses in the spinal cord at the level at which

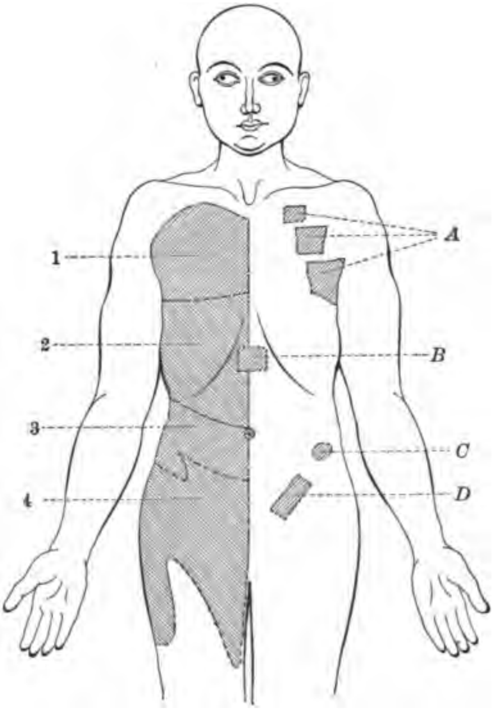
Increased flow = faster healing. Reduction of pain. Hypnotic suggestion
Locally stimulates process healing of chronic lesions (ex ulcers or corneal opacity)
+ bruises
& some skin
diseases

the fibres from the viscus and the superficial tissues meet, it is possible that new impulses reaching this area from the skin may alter its condition or may occupy a common path to the brain to the exclusion of impulses arising from the seat of disease.

Besides these physiological effects of counter-irritation, it must not be forgotten that a great impression is produced on the patient, and that some of the benefit may be due to hypnotic suggestion.

Therapeutic Uses.—Local irritants are applied occasionally to produce an alteration in the nutrition and blood supply of the skin itself and of the subcutaneous tissues. Thus in some chronic inflammatory conditions, with effusions into, or indurations of the subcutaneous tissues, the improvement of the circulation produced by slight irritation may be of benefit. An example of this is the treatment of ulcers of old standing with irritants. Another case in which a slight inflammatory attack causes very obvious improvement, is in corneal opacity, which may be removed entirely in some cases by the acute inflammatory reaction produced by such irritants as abrin. Probably a

FIG. 2.



The right side is divided into segments which correspond to some of the skin areas in which Head found tenderness in internal diseases. 1. Area of tenderness in disease of the lungs. 2. In diseases of the stomach. 3. In ovarian disease. 4. In disease of the Fallopian tubes and other appendages. On the left side are represented the points of application of counter-irritants in disease of the lungs (*A*), of the stomach (*B*), of the ovary (*C*), and the uterine appendages (*D*).

[illegible] neuralgia,
neuritis. In shock by effects on circulation. Mustard or cantharide
for effect on int. organs – blistering not necessary.

similar effect is produced on subcutaneous effusions, as in bruises. Some interesting experiments on this subject have recently been performed by Wechsberg, who induced suppuration in both hind legs of rabbits by the injection of irritants and then treated the one leg by the application of various irritants to the skin, while the other was left untreated as a control. He invariably found the abscess of the leg subjected to treatment less extensive and showing a greater tendency to heal than the other, and accounts for this by the œdema induced by the skin irritant diluting the original irritant and promoting its absorption. The increased blood supply leads to a larger number of leucocytes and more alexines around the inflammation than would otherwise be present. He found that the absorption of pigments from the rabbit's ear was much accelerated by the application of irritants to the skin over the part, and cites this as evidence that toxines are removed more rapidly under similar treatment. For these purposes only the milder irritants are required; in fact, vesication may do more harm than good. Mild irritation alters the sensitiveness of the sensory organs of the skin, and heat is often applied to alleviate pain and discomfort in the skin itself. In other instances pain is increased by heat, and, in fact, it is sometimes applied in the treatment of local anæsthesia, with the object of rendering the surface more sensitive. In many forms of skin disease, mild irritants are found to be of benefit; this is sometimes attributed to their antiseptic action, but the slight irritation is undoubtedly of some importance.

Counter-irritants are used in a large number of diseases, often without any definite idea of what precise effects they will elicit, but merely because they have been found to give relief in similar conditions. As a general rule they are placed over the affected organ, and this corresponds fairly in most cases of disease of the trunk with Head's area of skin tenderness. In the head, however, the segmental arrangement has been rendered very irregular by the compression in development, and counter-irritants are often found to be most effective when placed at some distance from the seat of pain, *e. g.,* behind the ear in some forms of facial neuralgia. They are used in acute inflammation of the lungs and pleura, in gastric disorders accompanied by much pain, in colic and in neuralgia and neuritis. Their action is very uncertain, but their application is often followed by great relief, more especially of pain. They are also used occasionally in shock or collapse, not for their effect on any individual organ, but to elicit the reflex alterations in the circulation which have already been described. A blister is often recommended in internal hæmorrhage, and may very possibly lessen the bleeding by altering the distribution of the blood in the organs, although it is difficult to estimate how far the improvement is due to the remedy and how far it is spontaneous. In order to produce any marked effect on internal organs, the more powerful irritants must be used, such as mustard or cantharides. It is not necessary, however, to produce actual vesication in the great majority of cases. Formerly blisters were opened and fresh irritants applied

Beware of counter irritation in patients of low vitality
" " also of heat & cold, poultices, baths etc

on the raw surface in order to prolong the effects, but this treatment was extremely painful, besides being liable to set up suppuration and ulceration, and it is very questionable whether any equivalent benefit followed.

Counter-irritation must be applied only with the greatest caution in weak, badly nourished, or very old persons, as it may cause sloughing. In diabetes, the tendency to gangrene contraindicates blistering, and in very young children only mild irritants are used.

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An enormous number of drugs produce irritation of the skin, and it would be idle to attempt to enumerate them here. In many instances, however, the irritant action is insignificant in comparison with the other effects produced, and these will, therefore, be discussed elsewhere; among these are found some of the alkaloids, the acids and alkalies, and many other inorganic preparations. Irritation of the skin may also be produced by heat and cold, and in fact burning in various forms was formerly used as a means of counter-irritation. Heat is still employed to cause irritation of the skin and subcutaneous tissues, and to promote their circulation. Thus, poultices and hot water compresses are beneficial in many local inflammations, though the same effects may generally be obtained by the use of the milder irritants. The effect of cold on the skin is more frequently demonstrated by bathing, and will be touched on in relation to the antipyrine series.

Apart from those drugs in which the irritation of the skin is merely an incident in a wider general action, there are a number of preparations which are used almost exclusively for this purpose. They may be divided into three classes: the volatile irritants, such as turpentine oil; the mustard series, some of which are also volatile; and those which are either non-volatile or only boil at high temperatures, such as cantharidin.

1. The Turpentine Oil Group.

Under the volatile irritants may be included a large number of the ethereal oils and many members of the methane and of the aromatic series; but among the ethereal oils those which possess a low boiling point, that is, those which contain a large proportion of terpene, with

Turpentine – bad blisters – in joints, sciatica, antiseptic, diuretic
Very active as hot stupes. Juniper also good diuretic

✓

comparatively little oxygen, are found to possess a more penetrating action than the others. At the same time, the taste and odor of these oils is often less pleasant than that of the others, so that they are less used as flavors and carminatives. The oils derived from the Coniferæ have, for this reason, been more largely used than the others for their effect on the skin, although several other volatile preparations are recognized by the pharmacopœia for this purpose. The action of these oils is similar in other respects to that of the general group (see p. 58), so that it need not be discussed here.

PREPARATIONS.

✓ **Terebinthina**, turpentine (U. S. P.), a concrete oleoresin obtained from Pinus palustris and other species of Pinus.

✓ OLEUM TEREBINTHINÆ (U. S. P., B. P.), oil of turpentine, a volatile oil distilled from turpentine.

✓ *Oleum Terebinthinæ Rectificatum* (U. S. P.), is formed from ordinary oil of turpentine by redistillation with lime water, in order to remove any acids and resin which may be contained in it. It consists of a mixture of terpenes ($C_{10}H_{16}$). Dose, 1 c.c. (15 mins.); as an anthelmintic, 8–15 c.c. (2–4 fl. drs.). 1cc. 4cc

✓ *Emulsum Olei Terebinthinæ* (U. S. P.), 4 c.c. (1 fl. dr.).

✓ *Linimentum Terebinthinæ* (U. S. P., B. P.).

✓ *Linimentum Terebinthinæ Aceticum* (B. P.), is formed by mixing turpentine, glacial acetic acid and camphor liniment.

Oleum Pini (B. P.), the oil distilled from the fresh leaves of Pinus pumilis.

✓ **Terebenum** (U. S. P., B. P.), a liquid formed from oil of turpentine by the action of sulphuric acid. It consists of a number of terpenes, one of which is the pure substance known as terebene. Its odor is more pleasant than that of turpentine oil, which it closely resembles in most other points.

✓ **Terpini Hydras** (U. S. P.), terpin hydrate, is a crystalline substance ($C_{10}H_{18}(OH)_2 + H_2O$) derived from oil of turpentine by the action of nitric acid in the presence of alcohol and water. It possesses almost no odor, is insoluble in water, and melts at about 116° C.

✓ **Sabina** (U. S. P.), the tops of Juniperus sabina, savine, contains as its active principle Ol. Sabinæ, a volatile oil which resembles that of turpentine in many respects, but is not identical with it.

✓ **Oleum Juniperi** (U. S. P., B. P.), oil of Juniper, is derived from the juniper berries and consists mainly of terpenes. Dose, 0.03–0.2 c.c. (½–3 mins.).

Spiritus Juniperi (U. S. P., B. P.), 1–4 c.c. (15–60 mins.). 1–4cc

Spiritus Juniperi Compositus (U. S. P.), 4–8 c.c. (1–2 fl. drs.).

In addition to these preparations the following may be mentioned here as possessing similar action and uses.

✓ *Linimentum Chloroformi* (U. S. P., B. P.).

✓ *Linimentum Camphoræ* (U. S. P., B. P.).

✓ *Linimentum Camphoræ Ammoniatum* (B. P.).

✓ *Linimentum Saponis* (U. S. P., B. P.), very slightly irritant.

✓ *Ceratum Camphoræ* (U. S. P.).

Therapeutic Uses.—Turpentine oil is used externally as a rubefacient, and differs from mustard and cantharidin in its greater penetrating power. It is not so irritant, however; it blisters only after long application, and the vesication produced is very painful and heals slowly, from the vapor penetrating into the deeper tissues. It is, therefore, employed to produce rubefaction only, and ought to be removed when this is attained. For this purpose any of the liniments

[illegible]. Sciatica. Antiseptic. Diuretic.

of the group may be employed, or a more intense action may be got from the "turpentine stupe," which is made by dipping flannel in hot water, wringing it dry, and then dropping warm turpentine oil on it.[1] Turpentine preparations are used especially in rheumatic affections of the joints or muscles, and in sciatica. The oleoresin may be formed into ointment, or plaster, and used as a feeble stimulant in skin diseases. Turpentine oil is a fairly strong antiseptic, and is less irritant than many of the more powerful ones. It is often inhaled in lung diseases such as tuberculosis or gangrene, and has the effect of lessening the odor in the latter; the oil may be simply allowed to evaporate, but is much more efficient when sprayed into the air. Many of the resorts for phthisical patients are stated to be rendered especially suitable for the treatment of this disease by the neighborhood of coniferous forests, which are supposed to dissipate the oils into the atmosphere; but this is probably only an insignificant factor in the treatment. Turpentine oil is occasionally added to baths in order to cause a slight general stimulation of the skin, which may be of benefit in some skin diseases and also in general debility under certain conditions; and pine-needle baths have some reputation in Germany for the same reason, the water being supposed to extract the oil.

Internally, turpentine oil is occasionally employed as a vermifuge, but is inferior to other preparations used for this purpose. A few drops are often added to purgative enemata to increase their efficiency. It has been given by the mouth in order to lessen flatulence and to disinfect the intestine in various diseases, among others, typhoid fever, although its value here is disputed. Preparations of turpentine oil and juniper are reliable and fairly powerful diuretics, but must not be prescribed in irritation of the kidney. The turpentine preparations have a certain reputation as expectorants, and terebene has been especially advised for this purpose; they are also given internally as pulmonary disinfectants. In some forms of neuralgia their internal administration has been found beneficial, and oil of turpentine has been used in internal hemorrhage, but with doubtful results. Old oil of turpentine was formerly advocated in phosphorus poisoning, but this treatment has proved to be valueless.

Along with these may be mentioned a series of resins which have some slight irritating effect on the skin, and have been used in the treatment of skin diseases.

Resina (U. S. P., B. P.), resin, colophony, is the residue left after distilling off the volatile oil from turpentine.

Ceratum Resinæ (U. S. P.).

Ceratum Resinæ Compositum (U. S. P.).

Emplastrum Resinæ (U. S. P., B. P.), adhesive plaster.

Unguentum Resinæ (B. P.).

Guaiacum (U. S. P.), *Guaiaci Resina* (B. P.), the resin obtained from

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[1] Alcohol has recently been applied in a similar way in phlegmon and other forms of inflammation. Gauze is soaked in alcohol (60–96 per cent.), wrung out, wound round the affected part and covered with cotton and oil-cloth.

Sinalbin + Myrosin (a ferment) = oil of mustard + Sinapine sulphate

Bad blister

Guaiacum officinale, contains several resinous acids, some volatile oils and gums. It is colored deep blue by oxidizing agents.

Tinctura Guaiaci (U. S. P.), 4 c.c. (1 fl. dr.).

Tinctura Guaiaci Ammoniata (U. S. P., B. P.), 2–4 c.c. (½–1 fl. dr.).

Mistura Guaiaci (B. P.), ½–1 fl. oz.

Trochiscus Guaiaci Resinæ (B. P.), each containing 3 grs.

Elemi resin (not official) is obtained from a number of trees of the order Burseraceæ, and contains volatile oil and resins.

Myrrha (U. S. P., B. P.), a gumresin obtained from Commiphora Myrrha (U. S. P.), from Balsamodendron Myrrha (B. P.), containing a small quantity of volatile oil.

Tinctura Myrrhæ (U. S. P., B. P.), 2–4 c.c. (½–1 fl. dr.).

Many other resins have been used in therapeutics, but have been abandoned, a fate by which these survivors seem to be threatened. They are occasionally used externally as mild irritant applications in skin affections. Galbanum, Ammoniacum, Guaiacum and Myrrh have been used internally for many different purposes, as expectorants, diaphoretics, diuretics, aperients, and have enjoyed a reputation in the treatment of amenorrhœa. They may be used to suspend insoluble bodies, as the gum contained causes them to form emulsions when water is added.

2. Mustard.

Mustard occurs in two forms in the pharmacopœias, Black Mustard, Sinapis nigra, and White Mustard, Sinapis alba. Black Mustard contains a glucoside, *Potassium Myronate* or *Sinigrin,* and a ferment, *Myrosin,* which decomposes it in the presence of water into dextrose, potassium bisulphate and allyl-isosulphocyanate or volatile oil of mustard.

$$\underset{\text{Sinigrin.}}{C_{10}H_{18}KNS_2O_{10}} = \underset{\text{Volatile oil.}}{CSNC_3H_5} + C_6H_{12}O_6 + KHSO_4$$

Volatile oil of mustard is formed in various other Cruciferæ when they are mixed with water. Thus horseradish root (Armoracia, B. P.) contains it, while the allied species Cochlearia officinalis apparently contains the corresponding isobutyl compound.

White mustard contains another glucoside, *Sinalbin,* which is also decomposed by the *Myrosin* in the presence of water. The products are entirely different, however, dextrose, sulphate of sinapine (an alkaloid), and an oil of mustard containing an aromatic nucleus being formed.

$$\underset{\text{Sinalbin.}}{C_{30}H_{44}N_2S_2O_{16}} = \underset{\text{Oil of Mustard.}}{C_6H_4(OH)CH_2NCS} + \underset{\text{Sinapine Sulphate.}}{C_{10}H_{23}NO_5H_2SO_4} + C_6H_{12}O_6$$

The oil of white mustard differs from that of the black in being less irritant, and in being destroyed by heat.

Action.—Either of these oils is intensely irritant when applied to the skin, and if left long enough produces blistering, which is more painful than that caused by cantharides, and is said to heal less readily. This is probably due to the oils penetrating more deeply into the tissues, and thus setting up more extensive inflammation. Mustard is accordingly used only to induce rubefaction, and ought to be removed before actual vesication occurs. When the crude drug is moistened and applied to the skin, the oil is formed only slowly, so

1 Tablespoonful mustard + 1 pint warm water = good emergency emetic
Charta Sinapis - mustard powder + India-rubber + paper.
15-30 min. for rubefaction. 60° + kills ferment.
In bath 2 tsps. for 1 gallon.

that the longer it remains applied, the more intense is the action. The glucosides in themselves have little or no action, and the products of their decomposition are harmless, with the exception of the oils.

PREPARATIONS.

Sinapis Alba (U. S. P.), **Sinapis Albæ Semina** (B. P.), the dried ripe seeds of Brassica alba.

Sinapis Nigra (U. S. P.), **Sinapis Nigræ Semina** (B. P.), the dried ripe seeds of Brassica nigra.

Sinapis (B. P.), a mixture of the powdered seeds.

CHARTA SINAPIS (U. S. P., B. P.), mustard powder rendered adhesive by India-rubber, applied to sheets of paper and dried. The U. S. P. preparation is formed from the black mustard, the B. P. from a mixture of the two.

Oleum Sinapis Volatile (U. S. P., B. P.), derived from black mustard.

Linimentum Sinapis (B. P.), formed from volatile oil of mustard, camphor and castor oil.

Uses.—Mustard is largely used as a condiment and to promote appetite, but is never prescribed for this purpose. In large quantities it causes violent irritation of the stomach and bowel, with vomiting, purging, acute pain and tenderness in the abdomen, and collapse. Mustard and warm water is a convenient emetic in emergencies, as in cases of poisoning. 1 tablespoonful in pint water

The plaster or leaf (charta) is the form in which it is generally used in therapeutics. It contains the glucoside, which is slowly decomposed by the ferment when the plaster is dipped in warm water for a few minutes before application. Another popular application is the mustard poultice, in which powdered mustard is sprinkled on an ordinary poultice. Mustard is also added to baths occasionally when slight irritation and consequent congestion is desired over a large surface. For this purpose 2–4 teaspoonfuls of the dry powder are added for each gallon of water. In preparations of mustard it is important to avoid a temperature of over 60° C. (140° F.), as the ferment is destroyed above this. The plaster is left on the skin only for 15 to 30 minutes, when it is used as a rubefacient.

3. Cantharidin Series.

Another series of local irritants comprises non-volatile substances, of which cantharidin is the best known. It is the anhydride of cantharidic acid, which does not exist itself, but the salts of which are formed from cantharidin by the action of bases. Cantharidin is represented by $C_{10}H_{12}O_4$, and is a derivative of benzol. It is found in Spanish fly (Cantharis vesicatoria, or Lytta vesicatoria) and in several allied species of Coleoptera (beetles). The irritant action of cantharidin and of many other drugs was formerly supposed to be due to its being an anhydride, but other anhydrides have no such specific action, and the cantharidates are quite as powerful as cantharidin.

Action.—Applied to the *skin*, cantharidin produces redness, smarting and pain, followed very soon by small vesicles, which later coalesce into one large blister. This is much less painful than the vesication

Cantharidin penetrates less deeply, so good for blistering. Cerate on adhesive plaster - 4-6 hours and replace [illegible] hot poultice. Renal inflammation by absorption possible

produced by mustard, because less of the irritant penetrates into the deeper tissues than in the case of the volatile mustard oil. If the blister be broken, however, and the unprotected dermis be allowed to come in contact with the irritant, violent inflammation with much pain, suppuration and even sloughing may follow.

When large quantities of cantharidin are given *internally,* the same irritant action takes place along the alimentary tract. If taken in solution, blisters arise in the mouth and throat, and the pain and swelling in the œsophagus may be so acute as to prevent swallowing. The irritation of the stomach produces vomiting, followed by purging with excruciating pain in the abdomen, and all the symptoms of shock and collapse.

Cantharidin is absorbed from the alimentary canal, and also to a less extent from the skin, but has no important action on the internal organs, with the exception of those by which it is eliminated. Vomiting occurs on subcutaneous injection, but the presence of ulceration of the stomach and of diarrhœa when it is absorbed from the skin, indicates that some of the poison is excreted into the alimentary tract, and the vomiting in these cases may therefore be of peripheral rather than of central origin. In the process of excretion, cantharidin has the same effects on the organs involved as on those of absorption. These effects are seen only in the genito-urinary tract in the vast majority of cases of poisoning. Comparatively small quantities irritate the bladder, and cause a constant desire to micturate, with pain in doing so. In somewhat larger amount it sets up an acute nephritis with albuminuria, pain in the kidney region, and sometimes blood in the urine. The inflammation of the bladder and urethra produces intense pain and often priapism; in women abortion is said to occur occasionally, and in both sexes the irritation may lead to increased sexual desire.

The irritation of the kidneys by small doses increases their secretion, and cantharides was therefore considered a diuretic formerly. The tendency to produce nephritis renders it a dangerous internal remedy, however, and its diuretic power is quite insignificant in comparison with that of caffeine.

Animals vary very considerably in the degree in which they react to cantharidin, the most noted example being the hedgehog, which is capable of surviving a dose of the poison sufficient to poison an adult man. Fowls and rabbits also possess a high degree of congenital tolerance for this poison, although none of these is absolutely insusceptible to it.

PREPARATIONS.

Cantharis (U. S. P., B. P.), Spanish Fly, the dried beetle, Cantharis vesicatoria.

CERATUM CANTHARIDIS (U. S. P.).

Collodium Cantharidatum (U. S. P.).

Tinctura Cantharidis (U. S. P., B. P.), 0.1–0.3 c.c. (2–5 mins.).

EMPLASTRUM CANTHARIDIS (B. P.).

EMPLASTRUM CALEFACIENS (B. P.), warming plaster.

Acetum Cantharidis (B. P.).
Unguentum Cantharidis (B. P.).
Collodium Vesicans (B. P.).
Liquor Epispasticus (B. P.).

Therapeutic Uses.—Cantharides is at present used almost exclusively as a skin irritant, and more particularly as a vesicant. In the United States the cerate is generally used for this purpose, and is applied to the skin by means of adhesive plaster; the corresponding preparation of the B. P. is the cantharides plaster. It is to be noted that in order to produce actual blistering, the plaster has to remain in contact with the skin some 8–10 hours, but an equal effect may be achieved by replacing the plaster by a hot poultice after 4–6 hours, when the skin irritation has reached the stage of redness. Cantharides is also used to cause rubefaction and commencing vesication (flying blister); this may be done by the use of these preparations, or by means of the warming plaster, B. P. Blistering collodion is used rarely in unmanageable cases in which there is a risk of the plaster being removed by the patient. The ointment is said to induce blistering sooner than the plaster.

Cantharidin is liable to be absorbed from the skin, and its application is therefore avoided where there is any tendency to renal inflammation.

Cantharides has been used not infrequently as an aphrodisiac, and several cases of poisoning have occurred from its administration for this purpose. In cattle it is largely employed to this end in some countries, and in man it has undoubtedly similar effects in some cases through the irritation of the bladder and urethra, but its use for this purpose is always liable to produce nephritis. As an emmenagogue, cantharides has a certain popular reputation, which however has been shown to be unmerited, any influence which it may possess on the menstrual flow being quite insignificant, and probably due only to the irritation of the bladder and urethra.

Cantharides has been advised internally in some forms of renal and vesical disease, but it is an exceedingly dangerous remedy in these conditions. In 1891, Liebreich proposed the treatment of tuberculous affections with cantharidinates, in the belief that these would cause an inflammatory reaction around the diseased nodules, and would thus lead to their being destroyed or encapsuled in cicatricial tissue. It has not been determined whether cantharidin acts more powerfully on irritated tissues, such as those around the tubercles, but experience has shown that no benefit followed Liebreich's treatment, while in several cases severe nephritis resulted from the injection, and the method has therefore fallen into disuse.

Cantharides is sometimes a constituent of hair washes, its irritant action on the skin being credited with causing a more rapid growth of the hair.

In cases of **Poisoning** with cantharides, the stomach ought to be emptied as rapidly as possible by the stomach tube, provided the œsophagus allows of its passage. Demulcents and albuminous substances are of use in slowing the absorption, but all oily or fatty bodies must be avoided, as they tend to dissolve the cantharidin and

Ivy poison due to [illegible] [illegible] [illegible] [illegible] in alcohol [illegible]. [illegible] in alcohol, which must be washed away. KMnO4 the best (+ [illegible]) [illegible] solution (St. Say)

thus promote its absorption. Opium may be given for the pain, and if collapse sets in, the ordinary measures must be taken to combat it. Ellinger states that the action on the kidney in rabbits is more severe when the urine is acid than when it is alkaline, and this suggests the treatment of the renal symptoms with alkalies.

Poison Ivy and Poison Oak.—The commonest form of poisoning in the United States is the skin eruption produced by the leaves of poison ivy and poison oak (Rhus toxicodendron and venenata) which Pfaff showed to be due to the presence of a neutral body, *Toxicodendrol;* this has recently been stated to be of glucosidal nature. The effects of poison ivy can arise only from touching the plant, the poisonous principle not being volatile. Very minute quantities of toxicodendrol are sufficient to produce skin eruptions, however, 1/1000 mg. causing distinct symptoms in susceptible persons. The popular belief that skin affections can be induced by approaching the plant, without actually touching it, is probably accounted for by the facts that the eruption may be very late in making its appearance, and that poison ivy is very frequently mistaken for harmless climbing plants. The statement that the poison ivy does not affect some individuals is also probably erroneous, though persons of delicate skin are undoubtedly more susceptible.

In the dermatitis from poison ivy, Pfaff recommends that the skin be washed and scrubbed with soap and water, or with alcohol, or a solution of lead acetate in alcohol. Ointments and oily liniments are to be avoided, as they dissolve the toxicodendrol and tend to spread it over the skin and thus produce further inflammation. For the same reason, the alcohol used to wash the part must be removed entirely, as the poisonous principle is soluble in it, while insoluble in water. Potassium permanganate solution is ~~said to be~~ an efficacious application.

Several little known substances may be classed along with cantharidin, which they resemble in their violently irritating effects on the skin and mucous membrances, and in being non-volatile. They are of little importance in therapeutics, but not infrequently give rise to accidental poisoning. A number of the Ranunculaceæ order are irritants, and this has been believed to be due to their containing *Anemonin,* $C_{10}H_8O_4$, which is closely connected to cantharidin in its chemical structure, but this has been disputed recently by Brondgeest, who asserts that this body is a convulsive poison. Noel and Lambert also state that anemonin is not the irritant contained in Anemone pulsatilla, which owes its irritant effects to some other more poisonous constituent. In Mezereum (Mezereum, U. S. P.), Buchheim found an anhydride which he termed *Mezerein,* but Springenfeldt states that the action is due to an oil and to the acid which it contains, which resemble croton oil and crotonoleic acid in their effects. *Cardol,* found in the fruits of Anacardium occidentale and in Semecarpus anacardium, is a very powerful irritant, and has been used to a limited extent as a vesicant. Cardol is probably a mixture of a number of substances, but it is unknown to which of these it owes its activity. *Euphorbin* is said by Buchheim to be the irritant principle in the Euphorbia resin (Euphorbia resinifera, etc.), and to resemble cantharidin in its anhydride form, but the salts and the euphorbic acid which is formed from them by acids are inactive, while the salts of cantharidic acid are irritant, and cantharidin is reformed when they are broken up by acids.

V.S. oils purg. but irritation of mouth, etc. Good purge is non-irritant to stomach & is absorbed slowly. Vegetable purgatives act thru their irritant properties — by after action on them by intest. secretions

A very poisonous member of the Euphorbiaceæ is the Manicheel tree, growing in the West Indies, and it apparently belongs to this series.

Capsicum (p. 76) contains one or more non-volatile irritant substances which probably resemble the principles of this series more closely than any other. Capsicum is used in small quantities internally and has therefore been mentioned along with the pepper series, but it is also used occasionally as a skin irritant. Pepper is also used as a rubefacient in domestic medicine.

Chaulmoogra Oil, obtained from Gynocardia odorata, is apparently similar in character to the members of this group, although it is less irritant. It is used externally as an application to bruises, and both externally and internally in leprosy, although it is probably of little avail in this disease. It is said to owe its activity to *Gynocardic acid,* which it contains in combination with glycerin. Croton oil is also used as a skin irritant, but will be treated of in connection with the purgatives (page 100).

Many other plants possess irritant, poisonous properties, which would apparently entitle them to a place in this series, but so little is known of their active principles and of their effects, that they may be omitted for the present.

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VII. VEGETABLE PURGATIVES.

Purgatives are drugs which are employed in medicine to evacuate the bowel of its contents. Many drugs produce evacuation in the course of their action, but have other effects of importance and are not included in this class. Thus the members of the preceding classes of skin irritants induce diarrhœa, but this is accompanied by irritation of the mouth, throat and stomach, and in many other forms of poisoning, diarrhœa is a prominent feature, but is accompanied by vomiting or some other symptom. The ideal purgative is devoid of any effects whatsoever, save in the intestine; it passes through the stomach without materially deranging its function, and is not absorbed, or at any rate is absorbed so slowly that it has time to unfold its action throughout the intestine. The vegetable purgatives act through their irritant properties, which in some instances are elicited only by the action of the secretion of the intestines and of the neighboring glands. Thus some of the purgatives pass through the stomach in the form of bland, non-irritant compounds (castor oil), which are broken up by the digestive processes in the intestine, while others perhaps owe their activity in the intestine to their solution or suspension in the juices.

Many classifications of the purgatives have been based on their effects, and some of the terms are still retained, such as *aperient, eccoprotic, laxative, purgative, cholagogue, hydragogue, cathartic or drastic.* But the effect of the purgatives is determined largely by the dose and by the condition of the intestine, so that a small dose may act as an aperient, laxative or eccoprotic, while a larger quantity of the same drug, or even the same dose in a more susceptible individual, may act as a drastic or hydragogue cathartic. It is, therefore, preferable to classify them according to their chemical nature as far as that is known, and in this way three classes may be formed, (1) purgative oils, (2) purgatives of the anthracene series, (3) the jalapin and colocynthin group.

Symptoms.—In moderate doses the purgatives simply hasten the normal movements of the intestines, and the stool is of the ordinary appearance and consistency (laxative, aperient, or eccoprotic action). In larger quantities they cause a more profuse evacuation than normally, and the stools, which are repeated at short intervals, are of a looser, more fluid consistency. Their action is accompanied by considerable pain and colic, and the hurried movements of the intestine are shown by the characteristic gurgling sounds. Large quantities of the more powerful purgatives may cause all the symptoms of acute enteritis; the stools at first contain the ordinary fæcal substances accompanied by more fluid than usual, but later consist largely of blood-stained mucous fluid with little or no resemblance to ordinary fæces. This violent purgation, which is not induced in therapeutics, is accompanied by pain and tenderness in the abdomen, and may induce shock, collapse and eventually death.

Action.—The origin of the fluid of the stools after purgatives has been much debated. According to many authors, they accelerate the passage of the intestinal contents so much that there is no time for the absorption of the fluid, and the fæces escape in the fluid condition in which they normally exist in the small intestine. Other investigators hold that purgatives cause fluid to pass into the intestine, either by increasing the normal secretions, or by causing an inflammatory exudate from the vessels. Both parties have founded, or attempted to confirm their statements by the results of the injection of the purgatives into loops of intestine isolated from the rest of the bowel. In these, some observers (Brunton, Roy) have found a larger accumulation of fluid after the injection of the purgatives, while others (Thiry, Radziejewski) found no more fluid after purgatives than after indifferent fluids. These contradictory results are probably due to the methods adopted, and the quantity of the drug injected. In small quantities, such as are used in the vast majority of cases in therapeutics, the irritation produced by the purgatives is probably only enough to accelerate peristalsis somewhat, and the fluid of the stools is drawn partly from the food and partly from the ordinary secretions of the digestive organs. In these cases the intestine is not actually inflamed, although some congestion may occur in it, as in all organs in a state of abnormal activity. On the other hand, when large

Small dose – no exudate – movements increased.
Large " = inf. "
Colic from rapid movements of intest + difficulty in forcing on hard feces
Irritation which causes local
reflex of Auerbach's plexus + muscular contractions

quantities are ingested a true inflammation of the intestine occurs, manifested by increased movement, congestion, the exudation of fluid into the lumen of the bowel, and pain. In these cases the intestine presents the usual signs of inflammation; it is red and congested, and contains a muco-purulent fluid and often blood. The matter, therefore, resolves itself into a question of dose; if it be small, the fluid is not an exudate, if it be large the fluid is partly an inflammatory product. The stools following the administration of purgatives differ from the normal fæces in containing a larger proportion of water and also of soluble substances. In fact, they resemble rather the contents of the small intestine than the normal excreta, and contain bodies which would normally have been absorbed and utilized but which have been hurried through the bowel too rapidly to permit of their being taken up by the epithelium.

The colic produced by purgatives is not due to the inflammation of the intestinal wall, but is probably explained by the more vigorous contractions of the walls of the bowel and the difficulty in forcing on hard fæcal masses in the large intestine. The tenderness produced by large quantities of the purgatives, on the other hand, would seem to indicate inflammation.

There is every reason to believe that purgation may be induced by reflexes arising from the stomach or skin, or from localized irritation of one part of the bowel; and these reflexes, in some instances at least, must pass by way of the central nervous system. In the accelerated peristalsis ordinarily induced by the purgatives, however, the central nervous system is probably not involved; the irritation of the mucous membrane renders it more sensitive to the stimuli which it ordinarily receives from the contents, and the nervous impulses resulting from these are transmitted to the intestinal nervous plexus and give rise to the reflex inhibition and contraction of the muscular coats by which the peristaltic movement is carried out. Magnus states that some purgatives (castor oil) act more especially on the small bowel, while others (senna) do not accelerate the movements here, but only those of the large intestine.

The action of the purgatives is generally considered purely local, and strictly analogous to that of the skin-irritants. The irritation of the epithelium and of the nerve-ends leads reflexly to increased activity of the deeper layers, which manifests itself in the bowel by contraction of the muscle, in the skin by hyperæmia. But some of the purgatives seem to have a further action, which is of a more specific nature. Thus senna, aloin, frangulin, and colocynthin cause evacuation of the bowel when injected subcutaneously or into the blood, podophyllum resin causes violent purging and vomiting when thus administered, and croton oil has long been rubbed on the skin in order to relieve constipation, and is found to cause intestinal inflammation and purging when injected intravenously. It has accordingly been suggested that these have a specific action on the bowel quite apart from their irritant effects; but it is quite possible that their intestinal effects are

2 - 24 hours. Leucocytes in intest blood increased, due to activity. No action on bile.

here due to their excretion into the bowel, which has been shown to occur in several instances. Other irritants applied subcutaneously or intravenously often produce similar effects on the alimentary canal.

The interval which elapses between the administration of a purgative and its effects varies with the dose, and also with the individual drug. In ordinary therapeutic doses, evacuation of the bowels occurs in most cases in 5–10 hours, but if large quantities of the more powerful purges, such as jalap or croton oil, be given, the effects may be elicited in two hours. Aloes and podophyllum differ from the others in the length of the interval, catharsis rarely or never occurring earlier than 10–12 hours after their administration, and often only after 20–24 hours.

The movement of the intestine induced by purgatives is accompanied by an increase in the leucocytes of the blood similar to that observed in other forms of intestinal activity, *e. g.*, during digestion.

The effects of the purgatives vary greatly in different animals. Thus, the rabbit is very refractory to most of the series, and often is killed by intestinal irritation without any evacuation being produced. The frog is unaffected by quantities which would produce poisoning in man, while the dog and cat respond much more readily.

It was formerly supposed that purgatives increased the secretion of bile, and certain of them, which were believed to have a special activity in this direction, were known as *Cholagogues*. It has been shown of recent years that none of them possesses any action on the secretion of bile, although they may increase its excretion by hurrying it through the intestine and preventing its reäbsorption. On the other hand, the presence of bile in the intestine is a condition necessary to the activity of many of the purgatives. Thus Buchheim and Stadelmann found that in the absence of bile the following purgatives are either quite inactive or very much less powerful than usual—podophyllum and podophyllotoxin, resin of jalap, convolvulin, resin of scammony, rhubarb, cathartic acid, and the sodium salt of gambogic acid. This is probably due to some solvent action of the bile, for Stadelmann found that when soaps were given with some of these drugs their activity returned, and in other cases a comparatively slight modification of their chemical form was sufficient to restore their activity, even in the absence of either bile or soap. Analogous results have been observed from other causes than the absence of bile; thus some of the pure principles of the purgatives are much less active than the crude drugs because the impurities of the latter alter their solubility. This alteration of the solubility may act in two ways: if the principle is rendered too soluble, it may be absorbed in the stomach and upper part of the bowel, and therefore fail to produce purgation; on the other hand, it may be rendered so insoluble that it fails to come into intimate contact with the bowel wall, and therefore does not irritate it. The effects of such colloid substances as the bile and gums is to delay the absorption of soluble substances in the upper part of the bowel and at the same time to keep the insoluble resins in suspension (Tappeiner).

Revulsion as intest inflamed + hyperaemic. In cerebral congestion
Congestion also in pelvis – abortion menstruation. Increased fluid
in intest – so less urine. Ricinoleic acid + ricinoleates formed
by intest juices from croton + castor
Ditto crotonoleic acid – tho some free in the oil

Few of the purgatives have any appreciable action after absorption, but general effects may be produced indirectly from their intestinal action. It is probable that reflexes are elicited by irritation of the bowel analogous to those discussed under skin irritants, but in addition, the congestion of the bowel produced by its activity must alter considerably the distribution of the blood in the body. The belief in the efficacy of a purge in congestion of the brain may thus be based on a true "revulsive" action; for the dilation of the intestinal vessels must necessarily lessen the blood pressure and thereby the blood supply to the brain. The congestion of the intestine is accompanied by a similar condition in the other pelvic organs, and the purgatives therefore often cause congestion of the uterus, with excessive menstrual flow, or in the case of pregnant women, abortion. Lastly, a certain amount of fluid is withdrawn which would otherwise be excreted by the urine, which is found to be proportionately diminished in amount.

1. The Purgative Oils.

Two very important members of the purgative series are *Castor oil* (Oleum Ricini), and *Croton oil* (Oleum Tiglii or Crotonis).[1] Castor oil consists almost entirely of an oil which resembles olive oil in most respects, but on saponification forms ricinoleic acid instead of oleic acid. This acid ($C_{17}H_{32}(OH)COOH$) differs from the fatty acids obtained from ordinary oils in being unsaturated and in containing a hydroxyl group. Castor oil is itself a bland, non-irritating fluid, but on passing into the intestine is decomposed by the digestive juices, and the ricinoleates thus formed are irritant and cause purgation. When the oil is saponified, and the free acid given by the mouth, the effects are quite different from those of the oil, for the taste is acrid and unpleasant, and discomfort, nausea and vomiting may follow its ingestion from its irritant action on the stomach. The oil, on the other hand, has a bland, if unpleasant, taste, and produces no effects on the stomach. Several other esters of ricinoleic acid have been shown by Meyer to resemble the glycerin ester (castor oil) in their purgative effects.

Croton oil is decomposed into glycerin and crotonoleic acid, of which little is known except that it is similar to ricinoleic acid from a chemical point of view. It differs from it in the fact that crotonoleic acid is a much more irritant body, and in that some acid is found free in the oil. This free acid renders croton oil irritant before it reaches the intestine, although the same process goes on here as in castor oil, and the croton oil therefore becomes more irritant than elsewhere. On the skin, and in the throat and stomach, croton oil exerts its irritant action, but these effects may be avoided while it continues to act as a purgative, if the free acid be removed. Croton oil then becomes bland and non-irritant, and can be distinguished from castor oil only by its more powerful purgative action. Castor oil is absorbed from the intestine and disappears in the tissues in the same way as an ordinary oil. Nothing is known with certainty of the fate of croton oil in the body, but it is not unlikely that it is excreted in part into the large intestine. Both croton oil and castor oil are borne in much larger quantities by animals than by man, and not infrequently the former causes acute enteritis without purgation.

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[1] Several other plants contain purgative oils, *e. g.*, Jatropha curcas, which bears the Barbadoes nuts, or purging nuts, and Garcia nutans and several species of Omphalea (Cash).

Castor oil may be given in very large quantities without producing any symptoms, save those of a mild laxative. Croton oil, on the other hand, acts as an irritant poison in any save the smallest doses, producing vomiting and violent purging with bloody stools, collapse and death. Castor oil is occasionally used as an emollient to the skin, and has been employed as a solvent for application to the eye, while croton oil has already been mentioned as a pustulant. The harmless nature of castor oil is shown by its use in China as an article of diet.

In the beans from which castor oil and croton oil are derived, toxalbumins are found, and these were at one time supposed to be the active principles of the oils. (See Ricin.) It has been shown, however, that the oils are entirely free from these poisons, and that their action is due solely to the acids of which they are glycerides.

PREPARATIONS.

OLEUM RICINI (U. S. P., B. P.), a fixed oil expressed from the seed, or bean of Ricinus communis. Dose, 4–30 c.c. (1–8 fl. drs.). 4–30c

Mistura Olei Ricini (B. P.), made up with cinnamon and orange flower water by means of mucilage, 1–2 fl. oz.

OLEUM TIGLII (U. S. P.), OLEUM CROTONIS (B. P.), a fixed oil expressed from the seed of Croton Tiglium. Dose, 0.02–0.05 c.c. (½–1 m.). .02–.05 c.c.

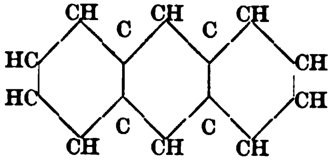
Castor oil is difficult to take owing to its unpleasant taste. It may be given alone, in an emulsion flavored with sugar and some volatile oil, in wine, spirits or glycerin, or in flexible capsules. in juice of 1 orange

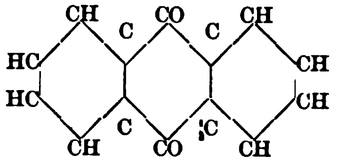
Croton oil is often given in a pill made up with bread crumb, or a single drop may be given on a lump of sugar or in solution in castor oil.

2. The Anthracene Purgatives.

A number of purgatives, *Rhubarb, Senna, Aloes, Cascara* and *Frangula,* owe their activity to the presence of irritant *anthracene* ($C_{14}H_{10}$) compounds, only a few of which have been isolated. The chemical examination of these drugs is a matter of great difficulty, as they each contain several active principles which are very nearly related to each other, and some of which are undoubtedly the products of the decomposition of more complex bodies. In addition, several of the pure substances have been found to be less certain in their purgative action than the crude drugs, probably because the colloids in the latter aid in their solution.

All those which have been completely isolated hitherto have proved to be derivatives of anthraquinone, Better action of alkaline.


Anthracene.


Anthraquinone.

and some of the oxyanthraquinones seem to be widely distributed. Thus all the members of the group contain *Emodin* or trioxymethylanthraquinone, $(C_{14}H_4(CH_3)(OH)_3O_2)$, and rhubarb and senna contain *Chrysophanic acid* or dioxymethylanthraquinone, $(C_{14}H_5(CH_3)(OH)_2O_2)$, while a nearly related body has been found in Frangula. It is still undecided whether the emodin found in different drugs is identical or merely isomeric, and the same may be said in regard to chrysophanic acid. In addition, a number of other anthracene bodies occur in these purgatives, some of them combined with sugars to form glucosides, but little is known regarding them, and it seems likely that some may prove to be impure emodin. Acid glucosides have been found in rhubarb, senna (*Cathartin* or *Cathartinic acid*) and in cascara and frangula (*Cathartin* and *Frangulin*). In the different species of aloes several *Aloins* (*Barbaloin* from Barbadoes aloes, *Socaloin* from Socotrine aloes, etc.) have been isolated.

Several of the pure principles have been used as purgatives, although they seem on the whole to be less certain in their effects than the crude drugs. *Chrysophanic acid* does not cause purgation, owing to its rapid absorption. *Frangulin* has given satisfactory results, and *Cathartin* has also been used experimentally, but is very liable to undergo decomposition. *Aloin* is less certain in its effects than aloes, and it seems to be indisputable that the crystalline aloin itself is inactive in the bowel, but is there changed under certain conditions to an amorphous compound which has irritant effects. This active substance can be prepared from aloin by boiling in water, and may be present in the amorphous resin left after the extraction of aloin. The purgative action of aloes is increased by the addition of small quantities of alkaline salts and of iron. The presence of bile in the intestine is not necessary to elicit the action of this group, except perhaps in the case of rhubarb; enemata of aloes are inactive unless bile is injected with them, but Kohlstock found that the same results could be attained by dissolving aloin in glycerin. The latter produces evacuation when injected alone as an enema, it is true, but he used smaller quantities of it than are necessary for purgation, so that the rôle played by the bile is probably the same as that of glycerin—a purely solvent one.

The absorption of these bodies has not been satisfactorily determined in most cases. The urine is rendered yellow after rhubarb and senna, owing to the absorption and excretion of chrysophanic acid, but it is questionable whether the more active principles pass into the urine in appreciable amounts. When aloin is injected subcutaneously or intravenously, it is excreted for the main part into the bowel, and there produces irritation and catharsis. Cathartin and frangulin also act as purgatives when they are injected subcutaneously, probably

Rhubarb contains tannin

because they are excreted into the bowel, although this has not as yet been investigated. The yellow pigment of the urine after rhubarb and senna becomes a purple red on the addition of alkalies; the milk and skin also are said to assume a yellowish tinge from the presence of chrysophanic acid.

In the rabbit aloin seldom causes purgation, and is excreted by the kidney in considerable quantity, especially when injected hypodermically. In passing through this organ it causes marked irritation and epithelial necrosis, which often proves fatal in a few days. No irritation of the kidney occurs in man, the dog, or the cat after aloin. Injected intravenously in animals, aloin induces powerful contractions of the uterus, apparently from direct action on the organ. The same effect probably occurs when it is absorbed from the alimentary tract, and its use is not advisable during pregnancy or menstruation.

Rhubarb contains a considerable amount of tannic acid, which acts as an astringent and therefore tends to cause constipation after the evacuation of the bowels. It is not well tolerated in some cases, its administration being followed by nausea, headache and giddiness, more rarely by skin eruptions of different kinds.

PREPARATIONS.

U. S. P.—**Rheum**, rhubarb, the root of Rheum officinale.

4 gr. EXTRACTUM RHEI, 0.25 G. (4 grs.).

Fluidextractum Rhei, 1 c.c. (15 mins.).

PILULÆ RHEI COMPOSITÆ (aloes, myrrh and oil of peppermint), 1–5 pills.

PULVIS RHEI COMPOSITUS (Gregory's Powder) contains magnesia and ginger. Dose, 1–4 G. (20–60 grs.).

4 *Tinctura Rhei*, 4 c.c. (1 fl. dr.).

Tinctura Rhei Aromatica (contains several volatile oils), 2 c.c. (30 mins.).

Mistura Rhei et Sodæ (contains bicarbonate of soda, ipecac, peppermint and glycerin), 10–100 c.c. (2 fl. drs.–3 oz.).

Syrupus Rhei
SYRUPUS RHEI AROMATICUS } Dose for child 4–10 c.c. (1–2 fl. drs.). 4-10 c.c.

B. P.—**Rhei Radix**, rhubarb root, the erect rhizome or so-called root of Rheum palmatum; 3–10 grs. for repeated administration; for a single administration, 15–30 grs.

PILULA RHEI COMPOSITA (contains rhubarb, Socotrine aloes, myrrh, and oil of peppermint), 4–8 grs.

PULVIS RHEI COMPOSITUS (Gregory's Powder) contains rhubarb, light magnesia and ginger, 20–60 grs.

TINCTURA RHEI COMPOSITA, formed from rhubarb, cardamom and coriander, ½–1 fl. dr. for repeated administration; 2–4 fl. drs. for a single administration.

SYRUPUS RHEI, ½–2 fl. drs.

U. S. P.—**Senna**, the leaflets of Cassia acutifolia (Alexandria Senna), and of Cassia angustifolia (India Senna).

CONFECTIO SENNÆ contains senna, cassia fistula, tamarind, prune, fig, sugar, and oil of coriander, 4–8 G. (1–2 drs.).

Fluidextractum Sennæ, 2 c.c. (30 mins.).

INFUSUM SENNÆ COMPOSITUM (Black Draught) contains senna, manna, 120 c.c. magnesium sulphate and fennel, 120 c.c. (4 fl. oz.).

4cc ✓SYRUPUS SENNÆ, 4 c.c. (1 fl. dr.).

Senna is also contained in the compound syrup of sarsaparilla and in the compound liquorice powder.

Senna is often administered as a simple infusion, senna tea, a teaspoonful of the leaves being used in a cupful of water.

B. P.—**Senna Alexandrina**, the dried leaflets of Cassia acutifolia.

Senna Indica, Tinnivelly senna, the dried leaflets of Cassia angustifolia.

TINCTURA SENNÆ COMPOSITA, formed from senna, raisins, caraway, and coriander, ½–1 fl. dr. for repeated administration; 2–4 fl. drs. for a single administration.

SYRUPUS SENNÆ, ½–2 fl. drs.

INFUSUM SENNÆ, ½–1 fl. oz.; as a draught, 2 fl. oz.

MISTURA SENNÆ COMPOSITA (Black Draught), formed from magnesium sulphate, liquorice, compound tincture of cardamom, aromatic spirit of ammonia, and infusion of senna, ½–2 fl. oz.

CONFECTIO SENNÆ, formed of senna, coriander, figs, tamarinds, cassia, prunes, liquorice, and sugar, 60–120 grs.

✓ U. S. P.—**Aloe**, the inspissated juice of the leaves of several species of aloe.

Aloe Purificata, aloes from which insoluble impurities have been removed, 0.25 G. (4 grs.).

Aloinum, a neutral principle obtained from aloes, 0.05 G. (1 gr.).

2gr. ✓EXTRACTUM ALOES, 0.1 G. (2 grs.).

PILULÆ ALOES, 1–5 pills.

PILULÆ ALOES ET FERRI, 1–5 pills.

Pilulæ Aloes et Mastiches, 1–5 pills.

Pilulæ Aloes et Myrrhæ, 1–5 pills.

Pilulæ Laxativæ Compositæ (aloin, strychnine, belladonna and ipecacuanha), 2 pills.

TINCTURA ALOES, 2 c.c. (30 mins.).

Tinctura Aloes et Myrrhæ, 2 c.c. (30 mins.).

Aloes is also contained in compound rhubarb pill, compound extract of colocynth, and compound tincture of benzoin.

B. P.—**Aloe Barbadensis**, the juice of Aloe vera and other species, Barbadoes Aloes or Curaçoa Aloes, 2–5 grs.

Aloe Socotrina, the juice of Aloe Perryi, Socotrine or Zanzibar Aloes.

Aloinum, ½–2 grs.

EXTRACTUM ALOES, 1–4 grs.

PILULA ALOES, 4–8 grs.

PILULA ALOES ET FERRI, 4–8 grs.

PILULA ALOES ET ASAFETIDÆ, 4–8 grs.

Pilula Aloes et Myrrhæ, 4–8 grs.

TINCTURA ALOES, ½–1 fl. dr. for repeated doses; for a single dose, 1½–2 fl. drs.

Decoctum Aloes Compositum (aloes, myrrh, saffron, potassium carbonate, liquorice, compound tincture of cardamom), ½–2 fl. oz.

Aloes is also contained in the compound extract of colocynth, compound colocynth pill, pill of colocynth and hyoscyamus, compound gamboge pill, compound tincture of benzoin and compound rhubarb pill. Some of the preparations are directed to be made from Socotrine, others from Barbadoes aloes, but there is really no difference in the effects.

U. S. P.—**Frangula**, Buckthorn, the bark of Rhamnus frangula, collected at least one year before being used.

Fluidextractum Frangulæ, 1–2 c.c. (15–30 mins.).

✓U. S. P.—**Rhamnus Purshiana**, Cascara sagrada, the bark of Rhamnus Purshiana.

¼g *Extractum Rhamni Purshianæ,* 0.25 G. (4 grs.).

1cc *Fludextractum Rhamni Purshianæ Aromaticum,* 1 c.c. (15 mins.).

Fluidextractum Rhamni Purshianæ, 1 c.c. (15 mins.).
B. P.—**Cascara Sagrada**, the dried bark of Rhamnus Purshianus.
Extractum Cascaræ Sagradæ, 2–8 grs.
Extractum Cascaræ Sagradæ Liquidum, ½–1 fl. dr.
Syrupus Cascaræ Sagradæ Aromaticus, ½–2 fl. drs.

Two artificial compounds of oxyanthraquinone have recently been introduced under the name of *purgatin* and *exodin*. They are quite insoluble in water and tasteless but are decomposed in the intestine and act there like the other purgatives. Purgatin colors the urine red and has some tendency to irritate the kidneys. Dose, 0.5–1.0 G. (8–15 grs.), in friable tablets or suspended in water. These bodies have no advantages over the natural purgatives and the possibility of their inducing nephritis renders their use inadvisable.

Of these numerous preparations, the most extensively prescribed are the pills. The fluid preparations have an unpleasant, bitter taste, and are therefore less used, unless when disguised by the addition of sugar or volatile oils. The syrups of rhubarb and senna are often administered to children, and the confection of senna and the compound liquorice powder are also pleasant, easily taken preparations. The compound infusion or mixture of senna and the compound rhubarb powder are old and tried preparations, in which the virtues of the vegetable purgative are combined with those of a saline cathartic and antacid respectively; they are both possessed of a harsh, unpleasant taste. Frangula is comparatively rarely used, but the fluid extract of cascara sagrada, which is practically identical with it, is a very popular remedy in habitual constipation.

Pure **Chrysophanic Acid** is not adapted for use as a purgative, as even in doses of 0.3 G. it fails to increase the peristalsis. A compound of chrysophanic acid, *Chrysarobin* ($C_{30}H_{26}O_7$), has found employment as an application in some forms of skin disease, especially in psoriasis, in which it is often of marked benefit. It is found in an impure form (Goa powder) in cavities in the Andira araroba, a tree growing in India and Brazil, and is isolated with comparative ease; it forms chrysophanic acid when it is oxidized. Chrysarobin is much more irritant than chrysophanic acid, and applied to the skin in a concentrated form, or in susceptible persons, causes itching, redness and swelling, less frequently papular or pustular eruptions; the skin and clothing are stained a reddish-brown color where it is applied. When swallowed, chrysarobin acts as a gastro-intestinal irritant, causing vomiting and purging; some of it is absorbed, and in its excretion by the kidneys causes in the rabbit nephritis with albumin and even blood in the urine. In man, slight albuminuria has been observed in some instances after its application to the skin; in animals the epithelium of the renal tubules has been found to be necrosed, the glomeruli being less frequently affected. It was anticipated that it would undergo oxidation to chrysophanic acid in the body, and this is true for a part of that absorbed, but most of it passes through the tissues unchanged. Pyrogallol apparently acts in the same way as chrysarobin in psoriasis, and the effect has in each case been attributed to the withdrawal of the oxygen from the diseased skin.

Araroba (B. P.), or Goa powder, a substance found in cavities in the trunk of Andira araroba, free from fragments of wood, dried and powdered.

Chrysarobinum (B. P.), a substance obtained from Araroba by extracting with hot chloroform, and evaporating. It consists for the most part of chrysarobin, but contains some chrysophanic acid.

Unguentum Chrysarobini (B. P.), 4 per cent.

Resinous glucosides. Active — rapid action, except podophyllum

Chrysarobin is used in skin diseases, especially in psoriasis, in which it is applied in ointment. Chrysophanic acid might be used also for this purpose were its isolation not attended with such expense. Some confusion has arisen from chrysarobin having been at first supposed to be chrysophanic acid.

3. The Jalapin and Colocynthin Group.

The third group of the vegetable purgatives comprises a number of resinous glucosides and acids, whose more intimate chemical structure is unknown, though a number of them appear to be nearly related chemically, so that it is possible that they all contain a common radicle like the members of the anthracene group.

Jalap resin contains two anhydride glucosides, *Convolvulin* and *Jalapin*, the latter only in very small quantity. Scammony consists very largely of *Jalapin*. Squirting cucumber contains a resin (elaterium), the active principle of which is *Elaterin*, another anhydride of which little is known. Podophyllum contains two isomeric glucosides, *Podophyllotoxin* and *Picropodophyllin* ($C_{23}H_{24}O_{9}$). Gamboge owes its activity to *Cambogic acid*, which, however, is insoluble, and seldom acts unless it is accompanied by the inactive bodies of the crude drug. *Colocynthin* is a glucoside occurring in the colocynth fruit, and forms *Colocynthein* and sugar when treated with acids. Colocynthein is said to be even more irritant than colocynthin. Euonymus owes its activity to a resinous glucoside, *Euonymin*. Many other plants contain similar resinous purgative substances, and some of these are used as remedies to some extent, but so little is known of their properties and they are so seldom employed that they may be omitted here.

Action.—These substances are in general much more powerful than any of the other purgatives except croton oil, and are therefore classed along with the latter as the drastic purgatives or hydragogue cathartics. In small quantities they cause evacuation more rapidly than the anthracene purgatives, and in somewhat larger doses produce profuse watery stools with much pain and often tenesmus. In cases of poisoning, the bowel undergoes acute inflammation, and blood is passed in the stools, which often contain shreds of epithelium from the walls. The irritant action is not confined to the bowel apparently, for their administration is sometimes followed by uneasiness in the stomach, and occasionally by nausea and vomiting. On the other hand, moderate quantities are said not to induce colic so frequently as some of the anthracene purges.

Several of these resinous purges are irritant to the skin and especially to the mucous membranes of the eye, nose and throat. Thus jalap, podophyllum and colocynthin all cause pain and irritation when they are applied to the nostrils in fine powder, and podophyllum has been used as a skin irritant.

The presence of bile in the intestine increases the purgative action of almost all these bodies, and in fact, seems absolutely necessary for the action of most of them. Some of them induce purgation when injected hypodermically, and this effect is not prevented by the absence of bile in the intestine.

Podophyllotoxin and colocynthin cause purgation when injected subcutaneously; this is probably owing to their excretion into the bowel, as the former has been detected in the fæces after this method of administration. Podophyllotoxin causes glomerular nephritis and hemorrhages into various organs when administered hypodermically or intravenously in large quantities, and when added to blood in a test-tube, it causes the formation of methæmoglobin in the corpuscles. It has been said to have a depressant action on the central nervous system, but this is probably a result of the shock and hemorrhage produced by its intestinal action. Colocynthin is said to cause renal inflammation when applied subcutaneously or taken internally, and even when the powder is inhaled during its manufacture. Jalapin and convolvulin given by the mouth cannot be found in the fæces or urine, and are therefore supposed to undergo partial or complete oxidation in the body. Convolvulin is found in the urine, however, when it is injected intravenously, and no purgation follows this method of administration; so that it is probable that convolvulin is decomposed in the bowel when it is administered internally.

Euonymin has the same effect on the heart as digitalis, and will be mentioned along with it, although it has a mild purgative action and is used chiefly as an aperient.

Preparations.

Colocynthis (U. S. P.), colocynth, the fruit of Citrullus Colocynthis deprived of its rind.

Colocynthidis Pulpa (B. P.), the dried pulp of the fruit of Citrullus Colocynthis freed from seeds.

Extractum Colocynthidis (U. S. P.), 0.03 G. (½ gr.).

Extractum Colocynthidis Compositum (U. S. P., B. P.) (containing colocynth, aloes, scammony and cardamom), 0.2–1 G. (3–15 grs.).

✓ Pilulæ Catharticæ Compositæ (U. S. P.) (compound extract of colocynth, jalap, gamboge and calomel), 1 pill as laxative; 3 as drastic purgative.

Pilulæ Catharticæ Vegetabiles (U. S. P.) (contain compound extract of colocynth, jalap, leptandra, podophyllum, hyoscyamus and oil of peppermint), 1 pill as laxative; 3 as drastic purgative.

Pilula Colocynthidis Composita (B. P.) (colocynth, Barbadoes aloes, scammony resin, potassium sulphate and oil of cloves), 4–8 grs.

Pilula Colocynthidis et Hyoscyami (B. P.) (compound pill of colocynth and extract of hyoscyamus), 4–8 grs.

Podophyllum (U. S. P.), **Podophylli Rhizoma** (B. P.), the rhizome and roots of Podophyllum peltatum.

Fluidextractum Podophylli (U. S. P.), 0.3–1 c.c. (5–15 mins.).

Resina Podophylli (U. S. P.), Podophylli Resina (B. P.), 5–30 mgs. 1/12–1/2 gr.).

Pilulæ Podophylli, Belladonnæ et Capsici (U. S. P.), 1 pill.

Tinctura Podophylli (B. P.), 5–15 mins.

Podophyllin varies considerably in composition, and ought to be avoided.

Podophyllotoxin. 5–10 mgs. Neither of these is pharmacopœial.

Jalapa (U. S. P., B. P.), the tuberous root of Ipomœa Jalapa. 0.3–1 G. (5–15 grs.).

Extractum Jalapæ (B. P.), 0.1–0.5 G. (2–8 grs.).

Resina Jalapæ (U. S. P.), Jalapæ Resina (B. P.), 0.1–0.3 G. (2–5 grs.). 2-5gr.

Pulvis Jalapæ Compositus (U. S. P., B. P.) contains jalap and bitartrate of potash. 1–4 G. (15–60 grs.).

Tinctura Jalapæ (B. P.), ½–1 fl. dr.

Scammonium (U. S. P.), a resinous exudation from the living root of Convolvulus Scammonia.

Resina Scammoniæ (U. S. P.), 0.2 G. (3 grs.).

B. P.—**Scammoniæ Radix**, Scammony root, the dried root of Convolvulus Scammonia.

Scammoniæ Resina, 3–8 grs.

Pilula Scammoniæ Composita (contains jalap and ginger), 4–8 grs.

Pulvis Scammonii Compositus (contains jalap and ginger), 10–20 grs.

Sluggish movements - short standing give castor, rhubarb, senna, aloes, cascara. Same in chronic constipation, but esp. diet or salines

Scammony is also contained in the compound colocynth preparations.

Euonymus (U. S. P.), **Euonymi Cortex** (B. P.), Wahoo, the dried root-bark of Euonymus atropurpureus.

Extractum Euonymi (U. S. P.), 0.05–0.2 G. (1–3 grs.).

Extractum Euonymi Siccum (B. P.), 1–2 grs.

Fluidextractum Euonymi (U. S. P.), 0.5 c.c. (8 mins.).

Elaterinum (U. S. P., B. P.), $C_{20}H_{28}O_5$, a neutral principle obtained from elaterium, a substance deposited by the juice of the fruit of Ecballium Elaterium (squirting cucumber). 1–5 mgs. ($\frac{1}{60}$–$\frac{1}{10}$ gr.).

Trituratio Elaterini (U. S. P.) (one part elaterin in 9 parts sugar of milk), 15–60 mgs. ($\frac{1}{4}$–1 gr.).

Pulvis Elaterini Compositus (B. P.) (one part elaterin in 39 parts milk sugar), 1–4 grs.

Cambogia (U. S. P., B. P.), Gamboge, a gum resin obtained from Garcinia Hanburii.

The resinous purgatives are generally administered in pill form; very frequently two or more are combined in one pill, or they may be prescribed along with extract of belladonna or hyoscyamus, or with a drop of some carminative oil or resin, to prevent the pain and griping which often accompanies their action. The importance of these purgatives is much less than it was formerly, and several of them are very seldom used; the most important are colocynth, podophyllum, and jalap. In large doses they act rapidly, with the exception of podophyllum, which induces purgation very slowly (10–20 hours).

Therapeutic Uses of the Purgatives.—The purgatives are employed to cause evacuation of the bowel when for any reason its peristalsis is slow. In ordinary constipation of short standing, in which the peristalsis may merely seem somewhat more sluggish than usual, the milder laxatives are prescribed—castor oil, senna, rhubarb, aloes, frangula, or cascara sagrada. The first two cause least disturbance of the bowel, but are disagreeable to take, and are less commonly prescribed for adults than rhubarb or cascara, or small doses of colocynth or podophyllum. In children or in debility in adults, senna and castor oil are frequently used however.

In chronic constipation which cannot be controlled by hygienic measures, or by the use of a special dietary such as fruits, or coarse meal, and where the intestine has apparently taken on a sluggish habit, rhubarb, cascara, aloes, podophyllum, or colocynth may be ordered, but the saline cathartics often prove more satisfactory. Rhubarb tends to cause some constipation after its laxative effects, but is often used in these cases, as it possesses some bitter stomachic action, which compensates for its astringent after-effects. This bitter action is often given to the other purgatives by the addition of gentian, nux vomica, or cinchona. In obstinate constipation, in which the bowel contains hard fæcal masses, the milder purgatives often provoke griping without relieving the condition, and in these cases larger doses of colocynth, jalap, podophyllum, or croton oil are used, along with some of the extracts of the atropine group or with a carminative oil. They may be prescribed along with some of the saline cathartics, as in the compound infusion of senna or the compound powder of jalap.

For revulsant effect, croton or jalap series.
Diuretics rather than ~~[illegible]~~ drastics to remove oedema.
Aloes in amenorrhoea.
Disinfectants — calomel esp.
Beware of purgatives in menstruation, hemorrhoids, pregnancy, circulation lesions. If necessary, castor, rhubarb, senna.

Croton oil is used especially where the drug is required to be of small bulk and the administration is attended with special difficulty; thus in unconsciousness or mania one or two drops may be given on sugar. In lead colic, croton oil is said to act more rapidly and efficiently than the others.

In some forms of diarrhœa constant irritation seems to be kept up by the presence of irritants in the bowel, and the indications are the removal of these by a purge rather than the administration of astringents. Castor oil, senna and rhubarb are especially adapted for this purpose; the two first because they increase the irritation of the bowel less than the others, the latter because of its subsequent astringent action.

A purgative is often administered as a preliminary in the treatment of malaria, syphilis and other conditions, and seems to have beneficial effects, although these are difficult to explain. In the beginning of acute fevers also a purge is often useful, perhaps through the congestion of the bowel withdrawing the blood from the rest of the body, or through the removal of poisonous substances formed by the decomposition of the intestinal contents. In congestion of the brain and in high blood-pressure a purgative is often administered with good effects, which may also be attributed to the accumulation of blood in the mesenteric circulation, and perhaps to some action analogous to counter-irritation of the skin. For these purposes a sharp purge is generally used, either croton oil or one of the jalapin and colocynthin series.

The more powerful purgatives, especially elaterium, were formerly largely used to remove fluid from the body in cases of dropsy or œdema, and they were generally prescribed along with the saline cathartics for this purpose. Other means, such as diuretics, are generally preferred now from a fear that the violent purging may weaken the patient, but good results are often obtained by means of this treatment, especially as a preliminary to the use of digitalis.

The specific action of aloes on the uterus, perhaps aided by the congestion of the pelvic organs from its purgative effects, had led to its use in amenorrhœa; it is generally administered along with iron or with myrrh, which is credited with some special action on the genital organs.

The purges act as intestinal disinfectants by removing the micro-organisms mechanically, though the vegetable purges are less used for this purpose than calomel. A purgative is administered to remove poisons in the intestine when they have passed beyond the stomach or when they are excreted into the bowel.

Purgatives are contraindicated in conditions of acute intestinal irritation, and during menstruation and pregnancy, owing to the congestion of the pelvic organs, which may lead to an excessive flow in the one case and to abortion in the other; aloes is especially dangerous in these conditions. In collapse, asthenia and anæmia, powerful purgatives are contraindicated, owing to the irritation they produce. In hæmorrhoids, aloes is often said to do harm by increasing the congestion of the rectum, and powerful purges are injurious from the straining they cause, but if constipation is present, a mild purgative is beneficial. In all those conditions, if a purgative is required, either castor oil, senna or rhubarb ought to be chosen.

Repeated attempts have been made to produce evacuation of the bowels by substances injected subcutaneously. Hiller found colocynthin the best available for practical purposes, although aloin and cathartinic acid also acted efficiently. The injection is so painful, however, that it ought only to be had recourse to in exceptional circumstances. Dixon has suggested the use of apocodeine for this purpose, and more recently some of the phenolphtalein compounds have been used by Abel and Rowntree.

Another method by which the purgatives may be administered is in enema. The addition of purgatives, such as castor oil, and of bile to the ordinary enemata has been practised for many years, but Kohlstock has recently drawn attention to the use of purgatives by enema with only 1–3 teaspoonfuls of fluid. The large water enema, containing a pint or more of fluid, acts mainly by distending the bowel and thus setting up peristalsis, although the soaps, salt and other similar bodies, which are often added to it, may have an irritating effect in addition. In the small enema, however, distention plays no part, the movement being elicited by the irritant action of the drug. Kohlstock found that colocynthin (0.01–0.03 G.), aloin (0.4–0.5 G.), and cathartinic acid (0.6 G.) dissolved in glycerin caused purgation, colocynthin acting in ½–2 hrs., aloin in 2–12 hrs. and cathartinic acid in 1–6 hrs. The two latter were certain in their effects only in cases of moderate constipation. He attributes their action to absorption from the rectum.

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Tannic acid in circ → gallic acid. Ta comp often contain sugar. Prec. albumins, glucosides, + all salts of Fe = ink. White prec with albumins + proteins, sol in excess alb. In acid sol pepsin + peptones not precipitated. Protein tannate + gastric juice = digestion → Ta + alb.

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VII. VEGETABLE ASTRINGENTS—TANNIC ACID SERIES.

A large number of vegetable substances owe their action to their containing tannin substances, while in many other preparations the effect of more important constituents is modified by the presence of these widely distributed bodies. Tannic acid proper ($C_{14}H_{10}O_9$) is a very feebly acid substance derived from the oak gall, and seems to consist of an anhydride combination of gallic acid, $C_7H_6O_5$, into which it ~~is very~~ easily decomposed. Gallic acid is formed from a large number of other bodies which closely resemble tannic acid in their general features, but are by no means identical with it. Their constitution is altogether unknown, but they possess a number of reactions in common and are generally classed together as the tannic acid substances. Some of them contain a sugar, and tannin or tannic acid is therefore sometimes said to be a glucoside. These bodies precipitate albumins, gelatin, alkaloids and some glucosides, and the salts of the heavy metals. The salts of iron form a bluish-black or greenish-black precipitate, and an attempt is sometimes made to divide the forms of tannic acid by this reaction, but they may be better indicated by their origin, as kinotannic acid from kino, catechutannic acid from catechu, etc.

Action.—The pharmacological effects of these bodies are due to their precipitating albumins and other proteins, and this reaction may therefore be described before their action in the body. If tannic acid solution be added to a neutral solution of albumin or gelatin, a white precipitate falls, which is entirely insoluble in water, but is soluble in excess of albumin or gelatin, in acetic or lactic acid, and in alkaline solutions.[1] Solutions of pepsin and of peptones are also precipitated by tannic acid unless in the presence of an acid. If protein tannate be exposed to the action of the gastric juice it undergoes digestion and is dissolved in the same way as an ordinary coagulated protein such as fibrin. During the process the tannic acid is set free from its combination apparently, and can precipitate undigested pro-

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[1] Some discrepancies in the accounts of different authors in regard to these reactions are perhaps due to variations in the amount of the neutral salts in their preparations.

Alkalis will satisfy acid radicle of tan. & then it won't prec. proteins
Constriction, dryness, roughness in mouth. In stomach prec. any protein but digestion goes on & won't prec. the peptone in acid, so prec. protein gastric mu[illegible]
(vomiting if extensive)

teins, although it has no effect on the peptones in the acid medium. When a soluble tannate is formed by the addition of soda or potash to a tannic acid solution, the presence of proteins produces no precipitate, the affinities of the acid being satisfied by the alkali, and for the same reason the tannic acid precipitate is dissolved in the presence of alkalies.

Tannic acid applied to animal tissue, as in the tanning of leather, causes a precipitation of the proteins, and the tissue becomes harder and tougher and tends to shrink together; at the same time it has less tendency to undergo putrefactive changes and does not lose its flexibility, as it would in drying. Strong solutions cause an immediate dense precipitate of the proteins on the surface and prevent the further penetration of the coagulating fluid, while the more dilute solutions are believed to penetrate more deeply and thus to cause a more complete precipitation of the proteins of the tissue.

Tannic acid solutions have a harsh, bitter, "astringent" taste and produce in the mouth a feeling of constriction, dryness and roughness, along with a sense of stiffness in the movements of the tongue, and some loss of taste. These effects are due to the coagulation of the superficial layers of protein both within and without the epithelium, which substitutes for the ordinary smooth surface a firmer, less even one, over which the tongue can no longer move easily. The feeling of constriction may, perhaps, be caused by an actual shrinking of the superficial layers of the epithelium, or may be due merely to the impaired movements and sensation.

The astringent feeling is continued in the throat as the solution is swallowed, and occasionally some discomfort or even nausea and vomiting are provoked by it, but as a general rule no such effects are observed. The stools are rendered harder and firmer by the administration of tannic acid, and constipation is often produced by it. In excess, tannic acid sometimes causes irritation of the intestine and diarrhœa, but beyond these symptoms of local irritation of the stomach and bowel, no effects arise from even enormous quantities of the drug.

In the stomach, tannic acid combines with any protein substance with which it may come in contact and precipitates it, but as digestion progresses, this combination is broken up, as the peptones do not combine with tannic acid in acid solution, and the astringent action is therefore exercised on the walls of the stomach and intestine. Ordinary quantities cause the same superficial coagulation as in the mouth, but if large doses be given when the stomach and intestine are not protected by foodstuffs, a more complete coagulation of the mucous membrane takes place and the consequent irritation results in vomiting, and sometimes in diarrhœa. The increase in the consistency of the stools is probably due to the layer of coagulated protein acting as a protective to the bowel, lessening its irritability and thus retarding its movements, so that there is longer time for the absorption of the fluid part of its contents, although this proceeds more slowly under tannic acid than normally (Gebhardt). The secretion of mucus by

Constipation as prec. proteins on stools, lessens irritation & peristalsis & increases absorption time. Mucous secretion lessened. Constriction then dil of vessels. Stops diapedesis. With blood – prec –. emboli. In feces & urine as gallic acid. Most is oxidized

the intestinal epithelium is lessened (Frey), and this may also retard the passage of the contents. Yeasts and microbes are precipitated by tannin, and this may tend to lessen the fermentation in the bowel in some cases, although some preparations of tannic acid which have been examined in regard to this point have been found to have little or no effect on intestinal putrefaction.

The local application of tannic acid causes a diminution of the secretions of glands, as has been demonstrated by Schütz. This is due to its effects upon the protoplasm of the secreting cells, which probably undergo the initial stages of coagulation.

It was formerly believed that tannic acid caused constriction of the vessels of any part to which it was applied, but some doubt has been thrown on this by the experimental results obtained by Rosenstirn and others. Heinz, the most recent writer on the subject, found that solutions of tannic acid of less strength than ½ per cent. caused constriction of the mesenteric vessels of the frog or rabbit when applied directly, while more concentrated solutions caused transient constriction followed by dilation. Another local effect produced by tannic acid is seen in the cessation of the movements of the leucocytes in the tissues around the point of application and the arrest of their diapedesis through the walls of the vessels.

When tannic acid comes in contact with blood in a test-tube it precipitates the proteins, and when it is injected intravenously, the precipitate formed leads to the formation of emboli.

The fate of tannic acid in the body has given rise to some discussion. When it is taken internally a small proportion is sometimes eliminated by the bowel unchanged, but very often none is to be found in the stools; traces are apparently absorbed and excreted in the urine in both man and animals, although some investigators have failed to detect these. When sodium tannate is administered internally, a distinctly larger amount of it is absorbed and reappears in the urine. But much the greater part of the tannic acid is decomposed in the intestine into gallic acid, some of which often passes out in the stools, some in the urine. Only about one per cent. of the tannic acid swallowed reappears in the excretions, either as tannic or gallic acid; the rest apparently undergoes complete oxidation in the tissues, for no further trace of it can be found. After tannic acid is administered, some tannic or gallic salt is present in the blood, for iron salts give a darker color to it, but it is impossible to state whether this is tannin or a gallate, although in all probability it is the latter. According to Harnack, the gallic acid in the urine sometimes forms pyrogallol on standing, but this poisonous substance is not formed from tannic acid in the intestine or tissues.

Tannic acid then does not exist in the tissues as such, but only in the form of traces of the gallate or tannate of soda, which are so small as to be devoid of astringent properties. Tannate of soda seems to have no action whatever, while gallic acid has no further properties than other weak acids. The effects of tannic acid are therefore lim-

So only local action. Gallic acid oxy in tissues.
Alkaline tannates inactive.

ited to the point of application, and there is no evidence of any weight that it exercises any action after absorption. The alkaline tannates are generally believed to be entirely devoid of astringent effects, but the tannic acid is freed to some extent by such feeble acids as carbonic acid, so that the astringent action is present in the intestine.

Tannic acid is often said to lessen the albuminuria in certain forms of Bright's disease, but the only exact determinations which have been made in man showed that no such effect was present, and in Ribberts' experiments the animals were moribund when the improvement occurred, and no safe deductions can be made therefore. The urine is sometimes said to be diminished by tannic acid, but this statement is based on error. Last of all, tannic acid is said to lessen internal hemorrhage by contracting the vessels, but tannate of soda, the only form in which it can exist in the blood is entirely devoid of action. Uses not

Gallic acid given by the mouth is absorbed and is excreted by the kidneys to some extent. Much of it disappears in the tissues, however, apparently by oxidation. Gallic acid has no astringent properties and is quite useless in therapeutics.

The numerous preparations of the pharmacopœias which owe their activity to their containing tannic acid, differ from the pure drug in that the acid is only slowly dissolved out from the colloid mass, and therefore acts less on the stomach and affects a greater length of intestine.

PREPARATIONS.

Acidum Tannicum (U. S. P., B. P.), tannic acid, gallotannic acid or digallic acid ($HC_{14}H_9O_9$), an organic acid obtained from nut gall, 0.1–0.6 G. (2–10 grs.). 2-10 gr.

✓GLYCERITUM ACIDI TANNICI (U. S. P.), GLYCERINUM ACIDI TANNICI (B. P.).

✓*Unguentum Acidi Tannici* (U. S. P.).

Collodium Stypticum (U. S. P.).

Trochisci Acidi Tannici (U. S. P.), 0.06 G. (1 gr.); (B. P.), ½ gr. in each.

Suppositoria Acidi Tannici (B. P.), 0.2 G. (3 grs.) in each.

Gambir (U. S. P.), an extract prepared from the wood of *Ourouparia Gambir*, 1 G. (15 grs.).

4 c.c. TINCTURA GAMBIR COMPOSITA (U. S. P.), (flavored with cinnamon), 4 c.c. (1 fl. dr.).

Trochisci Gambir (U. S. P.), each containing 0.06 G. (1 gr.).

Gambir has been substituted for the Catechu of former editions of the Pharmacopœia.

Catechu (B. P.), an extract of the leaves and young shoots of Uncaria Gambier.

2-4 c.c. TINCTURA CATECHU, ½–1 fl. dr.

Trochisci Catechu, each containing 0.065 G. (1 gr.) of catechu.

Pulvis Catechu Compositus contains catechu, kino, krameria, cinnamon and nutmeg, 10–40 grs.

Krameria (U. S. P.), Rhatany, the root of Krameria triandra and of Krameria Ixina, **Krameriæ Radix** (B. P.), the dried root of Para Rhatany (Krameria argentea?) or of Peruvian Rhatany (Krameria triandra).

03-1G EXTRACTUM KRAMERIÆ (U. S. P., B. P.), 0.3–1 G. (5–15 grs.).

Fluidextractum Krameriæ (U. S. P.), 0.5–4 c.c. (10–60 mins.).

Tinctura Krameriæ (U. S. P., B. P.), 2–8 c.c. (½–2 fl. drs.).

Syrupus Krameriæ (U. S. P.), 2–10 c.c. (½–3 fl. drs.).

Tannalbin (Ta + albumin + Δ) not digested by Stomach but by pancreatic juice

Trochisci Krameriæ (U. S. P., B. P.), each containing 1 gr.

Trochiscus Krameriæ et Cocainæ (B. P.), each containing $\frac{1}{20}$ gr. of cocaine.

Kino (U. S. P., B. P.), the inspissated juice of Pterocarpus Marsupium, 0.5–2 G. (10–30 grs.).

TINCTURA KINO (U. S. P., B. P.), 2–8 c.c. (½–2 fl. drs.).

PULVIS KINO COMPOSITUS (B. P.), contains 5 per cent. of opium, 5–20 grs.

Hamamelidis Folia (U. S. P., B. P.), Witchhazel, the leaves of Hamamelis Virginiana, contains tannin, a volatile oil and a bitter.

Hamamelidis Cortex (U. S. P., B. P.), the dried bark of Hamamelis Virginiana, witchhazel bark.

Fluidextractum Hamamelidis Foliorum (U. S. P.), 2 c.c. (30 mins.).

Extractum Hamamelidis Liquidum (B. P.), 5–15 mins.

Tinctura Hamamelidis (B. P.), ½–1 fl. dr.

Unguentum Hamamelidis (B. P.).

Hæmatoxylon (U. S. P.), **Hæmatoxyli Lignum** (B. P.), Logwood, the heart-wood of Hæmatoxylon campechianum.

Extractum Hæmatoxyli (U. S. P.), 1 G. (15 grs.).

Decoctum Hæmatoxyli (B. P.), ½–2 fl. oz.

Eucalypti Gummi (B. P.), a ruby-colored exudation, or so-called red gum, from the bark of Eucalyptus rostrata and some other species of Eucalyptus. 2–5 grs.

Trochiscus Eucalypti Gummi (B. P.), each containing 1 gr. of the gum.

Geranium (U. S. P.), Cranesbill, the rhizome of Geranium maculatum. 1–2 G. (15–30 grs.).

Fluidextractum Geranii (U. S. P.), 1 c.c. (15 mins.).

Rubus (U. S. P.), Blackberry, the bark of the root of Rubus villosus, R. Canadensis and R. trivialis.

Fluidextractum Rubi (U. S. P.), 1 c.c. (15 mins.).

Syrupus Rubi (U. S. P.), 2–8 c.c. (½–2 fl. drs.).

Galla (U. S. P., B. P.), Nut-gall, an excrescence on Quercus lusitonica (Quercus infectoria, B. P.), one of the oaks, caused by the punctures and ova of an insect, Cynips Gallæ tinctoriæ.

Tinctura Gallæ (U. S. P.), 4 c.c. (1 fl. dr.).

Unguentum Gallæ (U. S. P.).

Quercus (U. S. P.), white oak bark. 1 G. (15 grs.).

Fluidextractum Quercus (U. S. P.), 1 c.c. (15 mins.).

Several new preparations of tannic acid have been introduced into therapeutics of late years, chiefly for use as intestinal astringents. Tannic acid itself is liable to produce irritation of the stomach, and to be decomposed or absorbed to a large extent before it reaches the large intestine, and although the cruder preparations are less liable to these changes, even they are by no means devoid of disagreeable features. Meyer, therefore, introduced *tannigen*, or diacetyltannin, in which two of the original hydroxyl groups of the tannic acid are replaced by acetyl. This body is exceedingly insoluble in water, but is dissolved by alkalies. It was hoped that it would remain insoluble in the stomach and only commence to act in the bowel, and Rost finds that after administration by the mouth, it occurs in the human fæces in small quantity as tannic acid, while in the cat it passes through the alimentary canal in part unchanged. At the same time the presence of gallic acid in the urine indicates that part of it undergoes the fate of tannic acid. *Tannoform* is a somewhat similar combination of tannic acid and formaldehyde, while *tannopin* is a still more recent and untried member of the series. Both tannigen and tannoform are astringent in the mouth and stomach, but reach the bowel owing to their insolubility. The *tannalbin* of Gottleib, on the other hand, is a combination of tannic acid and albumen, dried at such a temperature as to prevent the action of the gastric juice upon it, but capable of being broken up by the more powerful pancreatic fluid. It is entirely us for excessive secretion. diarrhea. styptic. In poisoning precipitates metals + alkaloids.

insoluble and is not astringent until digested in the bowel, so that it has no irritant action on the stomach and is tasteless. Rost found tannalbin and tannic acid in the fæces of the cat after its administration, while only gallic acid occurs in the stools and urine in man, showing that in the latter the whole of the tannalbin administered is decomposed in its passage through the alimentary canal. *Tannocol* is a combination of tannic acid and gelatin, resembling tannalbin in most respects.

1 es TANNIGEN, 0.5–2 G. (10–30 grs.), in powder.
TANNALBIN, 0.5–2 G. (10–30 grs.), in powder.

Several combinations of gallic acid have been introduced of late years as astringents. They can have no such effect, however, and must be regarded as additions to the group of inert protective powders, which is already represented in overabundance in therapeutics.

Therapeutic Uses.—The preparations of tannic acid ought to be used for their local effects exclusively. They are applied externally in cases of excessive secretion, as in local sweating or weeping ulcers, and occasionally to harden the skin. For this purpose tannic acid may be used in solution in water, or in the form of the glycerite or ointment, or some other fluid preparation may be preferred. The styptic collodion may also be employed for this purpose, the evaporation of the solvent leaving the surface covered with a thin layer of collodion impregnated with tannic acid. Tannic acid is used as a mouth wash in cases of swollen gums, or relaxed throat, and may here be prescribed 24 in a flavored solution or in the form of lozenges, of which the pharmacopœia offers a choice. In certain forms of diarrhœa the astringent action of tannic acid is of considerable value, and occasionally when such drugs as cod-liver oil cause diarrhœa, tannic acid prevents this action without hindering their general effects. The pure drug is seldom used in these cases, as it is liable to derange the stomach and to form compounds with the albumins before it reaches the bowel, and catechu, krameria or kino is accordingly prescribed, either in the form of pills or in fluid preparations. Possibly all of these may be replaced in the early future by such artificial compounds as tannigen or tannalbin. Tannic acid stops hemorrhage by precipitating the proteins, when it comes into immediate contact with the bleeding point, but it is not of so much value for this purpose as some of the metallic astringents. When the bleeding point can be reached directly, the pure acid is used, but for hemorrhage of the intestine or stomach one of the extracts is preferred. Large enemata containing tannic acid have been advised in cholera, dysentery and similar conditions.

In cases of poisoning with metals and alkaloids, tannic acid is often used to cause ~~their~~ precipitation in the stomach, but the tannate formed must be removed at once, as it is gradually dissolved in the digestive fluids. The administration of tannic acid is therefore only a temporary expedient to allow of active measures being taken to empty the stomach.

Some individuals are peculiarly susceptible to the action of tannic acid, which induces local irritation and inflammation wherever it is applied in these cases.

[illegible] intestinal worms → : Specific act on parasite or failure of absorption, therefore in more concentration on parasite than host. Vermifuges, vermicides – expulsion or death – according to strength + rapidity of evacuation. Purge before + after. Naphthol, thymol

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IX. ANTHELMINTICS.

Anthelmintics are drugs which are used to kill or remove intestinal worms. Several of the members of this class present mutual resemblances in their chemical and pharmacological properties, while others may be classed with them as being used exclusively for this purpose.

In order to possess any value as an anthelmintic, a drug must, of course, act more strongly on the parasite than on the host, and this more intense effect may be attained either by a specific action on the parasite, or by the drug failing to be absorbed from the alimentary canal. As a matter of fact, the anthelmintics have not been shown to possess any such specific action, but seem to injure most forms of living matter; this has been demonstrated more particularly for muscle tissue. Their use is thus rendered possible only by their slow absorption, which permits of their acting on the parasite in greater concentration than on any of the tissues of the host.

Anthelmintics are often divided into vermicides and vermifuges, according as they kill or merely cause the expulsion of the worm, but as this is determined largely by the quantity which comes in contact with the parasite and the rapidity with which the bowel is evacuated, the distinction is imaginary.

Before the administration of an anthelmintic, the bowel ought to be emptied of its contents as far as possible by a light, easily digested diet and a laxative, and a brisk purge ought to follow some hours later, in order to remove the dead or stupefied worm. The anthelmintic is often prescribed along with a purge.

A number of drugs belonging to other groups are used occasionally as anthelmintics. Thus several of the volatile oils—tansy, turpentine—have some reputation; and chloroform is also administered occasionally by the mouth for its action on the parasites, but, like the volatile oils, is apt to produce gastric and intestinal irritation. The less easily absorbed antiseptics, such as naphthol, have been used with good results, and thymol is regarded as a specific in cases of unci-

If in large intest. — large saline enemata or infusions of quassia
In tapeworm male fern, cusso, pomegranate. In round worm santonin
Aspidium felix-mas (male fern). Extract or oleoresin kills tapeworm but
no effect on host. Some case of poisoning, sometimes blindness.

nariasis. Large enemata of salt solution, or of infusion of quassia, are thrown into the rectum when the worms infest the large intestines.

The anthelmintics proper may be divided into those which are used for tapeworm, of which *male fern, cusso* and *pomegranate* are the most largely used, and those for the round worm of which *santonin* is the chief. Besides these, an enormous number of substances have been used popularly as anthelmintics, but have not been shown to have any advantages over those more generally adopted in medical practice.

Male Fern (Aspidium Filix-mas).

A number of ferns contain bodies which present considerable resemblance to each other from a chemical as well as from a pharmacological point of view, and which may therefore be classed together, at any rate until further information is available regarding them. The best known of these is the male fern (Aspidium Filix-mas).

The active constituent of this remedy was supposed to be *Filicic Acid* by Poulsson, but Boehm has found other neutral and acid bodies present, *Aspidinin, Flavaspidic Acid, Albaspidin* and *Aspidinol*—and Kraft has added *Filmaron* and *Flavaspidinin*. These bodies are all derivatives of phloroglucin and butyric acid, and it is still uncertain whether the effects of male fern are to be attributed to any one of them or whether all of them may not share in the action. Jaquet holds that the chief therapeutic factor is the filmaron, but that the others also have some effect.[1]

Action.—The extract or oleoresin of male fern, which is the only one of these plants used in regular medicine, as a general rule passes through the bowel without causing any symptoms whatever. The quantity of active substance dissolved, while sufficient to destroy the parasite, is too small to produce any effects on the host, and escapes with the other contents of the bowel, or if absorbed does not cause any symptoms. In some cases, however, where large quantities are administered, or where some unknown conditions favor the absorption and retention of an unusually large amount of the active constituents, grave and even fatal symptoms may supervene. These consist in vomiting and purging, with acute pain in the abdomen, muscular weakness, confusion and somnolence, with occasional twitching of the muscles, or slight convulsive movements, collapse, coma and death. The stomach and intestine are found congested and swollen, and sometimes covered with small ecchymoses. In some cases icterus has been observed to follow the administration of male fern, probably from the duodenal catarrh, but possibly from destruction of the red blood cells, the number of which has been found to be diminished in some in-

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[1] Nearly related bodies have been found in Aspidium athamanticum (Uncomocomo), which contains two forms of *Pannic Acid,* and in Aspidium spinulosum, while smaller quantities of acids occur in a large number of ferns.

Several of these ferns enjoy a reputation as anthelmintics for tapeworm, and their virtues are generally considered due to these bodies, although Kobert maintains that it is partly to be ascribed to the fixed or volatile oils which accompany them.

Oleoresina Aspidii in pill. capsule or mucilage -(4-8 cc). In 6-12 hours give purge.

stances (Georgiewsky). In other cases permanent or temporary blindness has resulted from neuritis and subsequent atrophy of the optic nerve.

In the rabbit, filicic acid produces very similar symptoms. The congestion of the stomach and intestine is evidently due to the local irritation produced by the poison, while the other symptoms point to changes induced in the central nervous system. It would seem probable that the spinal cord is affected in the same way as by strychnine, for the reflex excitability is distinctly increased. The higher parts of the central nervous system seem to be depressed, and the paralysis of the respiratory centre is the cause of death, although the heart is also weakened by filicic acid. Inflammation of the kidney is said by some authors to occur, and in some cases Poulsson found evidence of glycuronic acid in the urine.

In the frog, a mixture of depression and stimulation of the central nervous system is produced by filicic acid, along with a distinct diminution in the strength of the skeletal muscles and the heart.

Aspidin (from Aspidium spinulosum) causes dyspnœa and paralysis of the spontaneous and respiratory movements in frogs; fibrillary twitching of the muscles sets in after some time and is succeeded by convulsive movements or tonic spasms, which indicate an increased activity of the reflexes of the spinal cord. The heart is depressed and eventually paralyzed, and the peripheral muscles are also weakened. The muscular tissue of the invertebrates is more powerfully affected by the constituents of male fern, and Straub attributes its action on the tapeworm to its paralyzing muscle. Mammals do not seem to be affected by aspidin injected hypodermically or administered by the mouth, but when it is introduced directly into the blood vessels, it proves fatal by paralyzing the respiratory centre. Aspidinin induces very similar symptoms in the frog, while the other constituents are less active.

The blindness which has been observed in some cases of male fern poisoning has also been produced in dogs; it occurs chiefly in young, weakly and anæmic individuals.

Pannic acid differs from filicic chiefly in its acting more strongly on muscle and less on the central nervous system of the frog.

PREPARATIONS.

Aspidium (U. S. P.), Male fern, the rhizome of Dryopteris Filix-mas and of Dryopteris marginalis, **Filix Mas** (B. P.), Male fern, the rhizome of Aspidium Filix-mas.

OLEORESINA ASPIDII (U. S. P.), 2–8 c.c. (½–2 fl. drs.). Pills, capsule, mucilage 2-8 cc

EXTRACTUM FILICIS LIQUIDUM (B. P.), 45–90 mins.

The oleoresin (U. S. P.) and the liquid extract (B. P.) are practically identical in composition.

Therapeutic Uses.—Male fern is used exclusively in the treatment of tapeworm and of Anchylostomum duodenale. Previous to its administration the bowel ought to be emptied, as far as possible, by a moderately light diet for one or two days and, where necessary, by a purgative. The oleoresin, or liquid extract, is then to be administered in the form of pills or enclosed in a capsule or suspended in mucilage, and another purgative is required some 6–12 hours later. In case the parasite fails to be dislodged, several days ought to be allowed to elapse before a second dose is given. Poulsson recommends that oily substances be avoided during the "cure," as they dissolve the active

Synergism: Aspidium poisoning + 1) debility or 2) alcoholism or 3) marked anemia.
Cusso resembles aspidium, Bitter + astringent. Sometimes vomiting & purgation
15 g) powder in H.O. Only for tapeworm

bodies, and thus promote their absorption. Other authorities dispute this view and some consider that oils in dissolving the active principles render them more poisonous to the parasites, but it is certainly suggestive that in many cases of poisoning with male fern castor oil had been given along with it or soon after. Marked anæmia, general debility and chronic alcoholism seem to predispose to male-fern poisoning, and the drug is accordingly to be used with care in these conditions.

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Cusso.

Cusso, or Kousso, contains a neutral body, *Kosotoxin*, which is soluble in alcohol and in alkaline fluids, but is insoluble in water; it is a compound of phloroglucin and butyric acid like the constituents of male fern, which it resembles somewhat in its pharmacological action. Cusso has a bitter, somewhat astringent taste, and sometimes causes nausea and vomiting and some looseness of the bowels. In rare cases prostration and collapse, with irregularity of the pulse, are said to have occurred from its use.

In the frog, kosotoxin paralyzes the nerve ends like curara, and has a specific action on the striped muscular tissue, which it weakens and eventually paralyzes. The heart muscle undergoes similar changes. In mammals the muscular action is well developed, but is accompanied by some stimulation of the medullary centres, indicated by rapid, dyspnœic breathing, salivation and vomiting. The stools are often fluid, and the urine is increased in amount. When it is injected directly into the circulation, some convulsive movements are often observed, and the heart is weakened and paralyzed. Kosotoxin seems to be a general protoplasm poison, as is indicated by its action on muscle, and by its retarding the growth of yeast.

Preparations.

Cusso (U. S. P., B. P.) (Kousso or Brayera), the female inflorescence of Hagenia Abyssinica (Brayera anthelmintica).

15g. in water

Cusso is generally given by suspending 15 G. (½ oz.) of the powdered flowers in water. Kosotoxin has not yet been prescribed for therapeutic purposes. The usual preliminary treatment ought to be instituted, but no purge is required after Cusso as a general rule.

Therapeutic Uses.—Cusso is used exclusively as an anthelmintic in cases of tapeworm.

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Granatum = Pomegranate. Large doses = giddiness & weakness. Much tannic acid (20%). Specific for tapeworms. Fresh granatum 30–60 g in 250 cc H_2O. in two parts, + flavor, taken at interval of 1 hour. Followed with purge in ½–2 hours

Granatum.

The bark of the pomegranate contains a very large amount of tannic acid (20–25 per cent.), along with several alkaloids, of which *Pelletierine,* or *Punicine,* and *Isopunicine* alone are active in ordinary doses. All the pomegranate alkaloids are closely related chemically to each other and to tropine (see atropine). None of them can be classed among the more active poisons as far as man and the higher animals are concerned.

In man, large doses cause heaviness, confusion, giddiness and very marked weakness of the limbs. The consciousness is but little affected, but the sight is often dim and uncertain, and in one case complete blindness persisted for several days. Occasionally nausea and discomfort in the abdomen are complained of, and more rarely vomiting, tremors and cramps of the leg muscles are produced; the gastric symptoms are perhaps due to the large quantity of tannic acid in the drug rather than to the alkaloids.

In the frog and in most mammals, pelletierine causes a distinct increase in the reflex irritability of the spinal cord and medulla oblongata, along with some depression of the higher divisions of the central nervous system. Very large doses weaken or paralyze the conductivity of the nerve plates in the frog, like curara. The heart muscle is also acted on and its pulsations are slowed in the frog, although they may be temporarily augmented in force.

Pelletierine and isopunicine have a specific action on tapeworms, for Schroeder found that a solution of one part in 10,000 was sufficient to kill them in ten minutes, while a stronger solution had practically no effect upon other intestinal worms.

PREPARATIONS.

Granatum (U. S. P.), **Granati Cortex** (B. P.), Pomegranate bark, the bark of the stem and root of Punica Granatum.

Decoctum Granati Corticis (B. P.), ½–2 fl. oz.

Fluidextractum Granati (U. S. P.), 2 c.c. (30 mins.).

Pelletierinæ Tannas (U. S. P.), a mixture in varying proportions of the tannates of four alkaloids (punicine, isopunicine, methylpunicine and pseudopunicine), obtained from the pomegranate. Dose, 0.25 G. (4 grs.).

Granatum is used as a decoction formed of 30–60 G. (1–2 oz.) in 250 c.c. of water (½ pt.), to be taken in two parts, at an interval of one hour. The bark ought to be as fresh as possible, as the alkaloids decompose on keeping. The presence of large quantities of tannic acid renders the decoction very unpleasant to the taste, and flavoring substances are therefore generally prescribed with it; or pelletierine tannate may be ordered.

Therapeutic Uses.—Granatum is used exclusively as an anthelmintic. The preliminary treatment is the same as that given under aspidium, and a purge ought to be given ½–2 hours after the decoction.

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Santonin insol in H_2O - santoninates with alkalies. If much absorbed = poisoning. ~~If~~ some always = yel urine. blue, then yellow vision (xanthopsia), then finally violet vision.

Tapeworm
2-8 G.
Intest irritant
Purge

Kamala is a reddish-brown powder which consists of the minute glands and hairs obtained from the surface of the fruits of Mallotus Philippensis. It contains two or more substances which have been termed *Kamaline, Rottlerin* or *Mallotoxin,* and which are probably neutral bodies like kosotoxin, but it is not known which of these is the active constituent. Kamala is used in cases of tapeworm in doses of 2–8 G. (30 grs.–¼ oz.) suspended in water. It acts as an intestinal irritant, causing purging and, more rarely, nausea and vomiting. No purge is necessary, therefore, after the powder. An alcoholic tincture of kamala has been found quite as efficient as the powder.

Pepo (pumpkin seed) contains a fixed oil and resin, and the latter seems to have considerable power as an anthelmintic, although this is disputed by some authorities. No symptoms are produced by very large quantities of the powdered seeds.

Pepo (U. S. P.), the seed of Cucurbita pepo, Pumpkin seed, is generally administered in doses of 60–120 G. (2–4 oz.), the powdered seed being suspended in an emulsion or in sugar or honey. Pumpkin seed has no laxative effect and its administration is, therefore, to be followed by a purge. The resin has been used with good effects in some cases.

Areca Nut, the seeds of the palm Areca Catechu, is used in veterinary medicine as a remedy in tapeworm. It contains a fluid alkaloid arecoline ($C_8H_{13}NO_2$), which acts like pilocarpine when given in large doses. In addition, it contains several inactive alkaloids and tannic acid.

Santonin.

Santonin ($C_{15}H_{18}O_3$) is an anhydride or lactone of santoninic acid, which is formed from it by the action of alkalies, and is a derivative of naphtalene. It occurs in Artemisia pauciflora along with a nearly related body (artemisin) and a volatile oil (cineol). Santonin is very insoluble in water, but is dissolved by alkalies, with which it forms santoninates.

Action.—Owing to its insolubility in water, santonin has only a slightly bitter taste in the mouth. It is partially dissolved in the stomach and absorbed, but enough passes into the bowel to effect the removal of some forms of intestinal worms. Under special conditions it is possible that the greater part of the santonin may be absorbed in the bowel, however, and general poisoning results without the parasites being affected. A certain amount of absorption occurs in every case, as is shown by the disorders of color vision and by the yellow coloration of the urine. At first objects appear of a bluish color to the patient, but this aberration is of comparatively short duration and may in fact pass unnoticed. It is followed by a much longer period of "yellow sight" or xanthopsia, during which objects that are brightly illuminated seem to have a yellow tinge, blue seems green, and violet is indistinct, although in dimmer lights the violet may still predominate. In severe poisoning the appreciation of the darker colors becomes very imperfect, and violet and even blue may fail to be distinguished from black. In general the violet end of the spectrum is shortened, while the yellow impresses the retina more vividly than normally. Sometimes "hallucinations" of vision are said to occur under santonin, although these seem to be unimportant; thus one observer saw green globes on a violet background whenever he closed

Sym. of poisoning ✓

his eyes. These aberrations of sight are the most generally observed symptoms produced by santonin, but in some cases the senses of taste and smell, and more rarely the hearing, are also deranged. These symptoms all pass off in the course of a few hours, a second stage of "violet sight" occasionally intervening before complete recovery.

The symptoms produced by the absorption of large quantities of santonin are so uniform in man and the other mammals that it is sufficient to enumerate those observed in experiments on the dog. The first distinct effects are generally twitching of the muscles of the head, frequently beginning on one side. These are followed by rolling of the eyes, grinding of the teeth, flexion and extension of the neck and rotation of the head from side to side, later by regular epileptiform convulsions in which the animal is first thrown into opisthotonos and then into clonic spasms of the limbs and trunk. These are interrupted by intervals of repose during which a curious momentary contraction of all the muscles of the body is often noticed. During the convulsive seizures the respiration is irregular and insufficient, and in fatal cases it fails to return after the convulsion passes off, and the animal dies of asphyxia. In man, some confusion, nausea and vomiting occasionally occur after quantities which are too small to produce convulsions, and in several cases aphasia has been observed. In frogs, convulsions are produced by santonin as in mammals, but they are preceded by a prolonged stage of depression, which is entirely absent in the higher animals.

These symptoms manifestly point to changes in the central nervous system. The xanthopsia is generally referred to a specific action on the retina, though some hold that the central apparatus of vision in the brain is the seat of the action.[1] The condition has been ascribed to a preliminary stimulation and subsequent depression of the sense organs for the perception of the violet and eventually of the blue rays of the spectrum, or more precisely to some obstruction to the regeneration of the substance in the retina which normally appreciates violet rays (Filehne). The clonic nature of the convulsions at once points to an affection of the brain rather than of the cord, but some discussion has arisen as to how far the cortical areas are involved and how far the symptoms may be explained by stimulation of the basal ganglia. The latest investigators have come to the conclusion that the epileptiform convulsions are due for the main part to the stimulation of the cortex, while the sudden contractions observed in the intervals of repose are ascribed to increased activity of the parts lying between the cerebral peduncles and the medulla oblongata. The gray matter of this division of the central nervous system also seems involved in the clonic movements, although these are only elicited in their full strength through action on the cerebral cortex (Kramer).

Although these parts of the central nervous system are the most susceptible to the action of santonin, large quantities also affect the

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[1] The view formerly held that the yellow vision was due to a yellow pigmentation of the vitreous humor or the retina is undoubtedly erroneous.

Oxidation + elimination in feces + urine as oxysantonins. Yellow + alkalies = red. Same reactions for chrysophanic acid from rhubarb and senna. Used for Ascaris lumbricoides - round worm. Not death, but disgusted

cord after division of the medulla oblongata and produce tonic convulsions resembling those seen in strychnine poisoning.

The medullary centres seem to be comparatively little affected by santonin, the respiration being interfered with during the spasms, but returning to its ordinary rate and strength during the intervals. The circulation is altered only by the asphyxia, and the heart continues to beat long after the respiration has ceased.

Santonin undergoes some oxidation in the tissues and is excreted in the fæces and urine in several forms, two of which have been examined by Jaffe and found to be oxysantonins. The urine and sometimes the fæces have a deep yellow color, which changes to red or purple when alkalies are added. A similar reaction is obtained from the urine after the administration of chrysophanic acid, as in rhubarb or senna, and a number of reactions are given to distinguish between these two pigments, which, however, it can scarcely be necessary to do frequently.[1]

Santonin is universally used as a remedy for the round worm, Ascaris lumbricoides, and most clinicians believe that it has a specific poisonous action on these animals, and that its undoubted effects are due to its killing them. In experiments on the entozoa outside the body, however, von Schroeder found that santonin solutions were by no means fatal to them, and he explains their therapeutic effects by supposing that santonin renders the intestine so unpleasant an abode for the parasites that they migrate from it voluntarily into the large bowel, and are carried out by the purgative. The worms are often found in active movement when passed after santonin, although this movement ceases very soon afterward from the exposure to cold.

The alkaline salts of santoninic acid act in precisely the same way as santonin itself, but are less suitable as anthelmintics, owing to their greater solubility and rapid absorption.

PREPARATIONS.

.03 - .1 G
gr. 1/2 - 2 gr

SANTONINUM (U. S. P., B. P.), $C_{15}H_{18}O_3$, a neutral principle derived from Artemisia pauciflora, is colorless when freshly prepared, but assumes a yellow color when exposed to the light. This does not seem to impair its activity materially, but it is preferable to avoid it by keeping santonin in amber-colored vials. Dose, 0.03–0.1 G. (½–2 grs.).

1/2 gr

TROCHISCI SANTONINI, each containing 0.03 G. (½ gr.) of santonin, U. S. P.; ~~each containing 1 gr., B. P.~~ 2 for adults

Therapeutic Uses.—Santonin is used almost exclusively to remove Ascaris lumbricoides from the intestine. It is much less effective against tapeworm or other intestinal parasites. The lozenges are generally prescribed, one for children, two for adults, U. S. P., while the dose of the B. P. lozenge is one for an adult. Lewin recommends

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[1] Thus the red of chrysophanic acid is permanent, while that of the santonin pigment fades after a time, and reducing agents, such as zinc, remove the former, and not the latter, while barium and calcium precipitate the chrysophanic and not the santonin pigment.

Purge in 2-4 hours. Dose two ½ gr troches for adults. Stomach pump; purges or enema when poisoned. Control convulsions with ~~ether~~ or chloroform. Xanthopsia not a poison symptom

the administration of santonin in oily solutions, especially in castor oil, as less is absorbed from the stomach than when it is prescribed in other ways. The bowel ought to be emptied by suitable diet and a laxative before the santonin is administered, and a sharp purge ought to be given 2–4 hours afterwards in order to bring away the entozoa.

Santonin has been advised in some retinal diseases, but the results have generally been unsatisfactory.

Poisoning.—In cases of poisoning, the stomach and bowel ought to be evacuated as rapidly as possible by the use of emetics or of the stomach tube, and of purgatives or enema. The convulsions may be controlled by the use of chloroform or ether. The xanthopsia requires no treatment, and is not to be regarded as heralding any dangerous developments, as it occurs to some degree in the great majority of cases in which santonin is administered.

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SPIGELIA.

Another remedy used in cases of round worm is pink root, Spigelia maritima, the active principle of which is unknown, although an alkaloid, *spigeline,* is said to occur in it. Occasional cases of poisoning have been observed, especially in children, the symptoms consisting in flushing and dryness of the skin, often with some œdematous swelling of the face, delirium and sopor followed by dimness of sight or temporary blindness. In frogs spigelia appears to depress the brain and spinal cord, and the heart beats more slowly and weakly, while in rabbits the most prominent symptoms arise from the breathing, which becomes slow and labored and finally ceases in a convulsive attack. In the dog and cat its injection is followed by vomiting, great weakness and incoördination of the movements, restlessness, rapid dyspnœic respiration and finally by stupor, coma and death from failure of the respiratory centre.

Spigelia (U. S. P.), the rhizome and roots of Spigelia marilandica.

Fluidextractum Spigeliæ (U. S. P.), 4–8 c.c. (1–2 fl. drs.).

The fluidextract is used to remove round worms, which it seems to effect in very much the same way as santonin. It ought to be preceded and followed by a purge.

One of the volatile oil series which is frequently used as an anthelmintic is that obtained from **Chenopodium** ambrosioides or American worm-seed.

Oleum Chenopodii (U. S. P.), 0.2–0.3 c.c. (3–5 mins.). The oil is administered on sugar or in an emulsion.

Action (depressant) on c.n.s., esp. cerebrum. Sol. in CNS! lecithin + cholesterin + impair their function = narcosis.

PART II.

ORGANIC SUBSTANCES CHARACTERIZED CHIEFLY BY THEIR ACTION AFTER ABSORPTION.

I. NARCOTICS OF THE METHANE SERIES.

ALCOHOL-CHLOROFORM GROUP.

A LARGE number of the derivatives of the methane series are characterized by the production of depression of the central nervous system, more especially of the cerebrum, and some of them are perhaps the most extensively employed of all drugs. With the exception of alcohol, which has been known since prehistoric times, the use of the members of this series scarcely extends over more than half a century.

From the large number of substances belonging to this division of organic chemistry which are possessed of narcotic powers, it would seem that the combination of carbon and hydrogen in the form characteristic of this series is possessed of a special relation to the protoplasm of the nerve cells, or in other words, carbon radicles combined in open chain form are possessed of specific depressant powers. As a general rule the greater the number of these radicles contained in the chain, the more powerful the action, provided the substance is not changed so as to become incapable of absorption. Thus, in the alcohol series a regularly ascending scale of toxicity is met, commencing with methyl and ethyl and passing through propyl, butyl and amyl alcohols, of which each succeeding member is more poisonous than its predecessor. The later members of the series, however, become less soluble in the body fluids, are less easily absorbed, and therefore less toxic.

A very interesting hypothesis has recently been suggested by Meyer[1] and Overton[2] to explain why so many of the bodies of this series act as narcotics. Practically all of them are more soluble in lecithin and cholesterin than in water and accordingly when they reach the blood they tend to accumulate in the nerve cells, which are rich in cholesterin and lecithin. Here they may be supposed to dissolve partially these constituents, or, at any rate, to change their relations to the rest of the nerve cells and this derangement of their normal condition leads to impairment of the function of these cells, or narcosis. But many other substances (*e. g.*, many of the benzol derivatives) possess these physical properties equally with the members of the methane series,

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[1] Arch. f. exp. Path. u. Pharm., xlii., p. 109, and xlvi., p. 338.

[2] Studien u. d. Narkose. Jena, 1901. *Gottlieb.* Ergeb. d. Physiol., i., 2, p. 666.

The more [illegible] the [illegible] point
[illegible] then narcotic power decreases
the more OH radicles the more the substance [illegible] in [illegible] rather than
in its [illegible]. +acid [illegible] has no [illegible] power.

Ethyl alcohol, ethyl ether, ethyl chloride, chloroform

and yet induce no narcosis proper, so that though the physical characters of these drugs may probably be important factors in their action, they cannot be held to determine it solely. It seems likely, therefore, that their solubility in the lipoids enables the bodies of the methane series to penetrate into the nerve cells, and that there they exercise some influence which is not directly due to this factor of solubility. The derivatives of the benzol series which resemble them in their solubilities also penetrate in the same way presumably, but fail to act in the same way after reaching the interior. Changes in the molecule of methane derivatives may deprive them of their depressant action by preventing their penetration into the cell. Thus the presence of an acid radicle in the molecule renders it more soluble in the fluids surrounding the cell than in the cell lipoids and prevents its penetration, and propionic acid (CH_3—CH_2COOH) has therefore no narcotic action, while both propyl alcohol (CH_3—CH_2—CH_2OH) and ethyl alcohol (CH_3CH_2OH) are depressants to the central nervous system. In the same way, glycol (CH_2OH—CH_2OH) is much less active than ethyl alcohol (CH_3—CH_2OH), because with the increase in hydroxyl groups the solubility in lipoids decreases and that in water increases and there is thus less tendency for the molecule to leave the lymph for the interior of the cell; a still more striking example of this is seen in glycerine, in which there are three hydroxyl radicles and which is devoid of narcotic properties.

It is impossible to enumerate here all the substances of this series which possess more or less depressant action on the nerve centres. A very large number of them have been the subject of investigation, but only a few of them have become established remedies.

Among the *hydrocarbons* the fifth, **Pentane**, and the eighth, **Octane**, have been proposed as anæsthetics for short operations, but have never received an extensive trial. Some of the *unsaturated hydrocarbons* have also been suggested, such as **Amylene**, which was introduced by Snow, but was found to vary exceedingly in its properties, and proved to be a mixture of several isomers. One of these has been used for short operations under the name of **Pental** ($(CH_3)_2 = C = CH - CH_3$). Another unsaturated hydrocarbon which has been shown to possess narcotic properties is **Acetylene**, but its action on the heart is said to preclude its use in practical therapeutics.

Among the *alcohols*, **Ethyl alcohol** (C_2H_5HO) stands preëminent from its extensive use in therapeutics as well as from its importance in dietetics and as a poison. Other alcohols have been found to resemble it in action, but the only one that has been introduced into therapeutics is **Amylene hydrate**, or tertiary isoamyl alcohol ($(CH_3)_2C(OH)CH_2CH_3$), which has been recommended as a hypnotic.

The *ethers* contain one very important member in **Ethyl ether** ($(C_2H_5)_2O$), which is perhaps the best anæsthetic in use.

The *aldehydes* possess narcotic properties, but ordinarily are irritant and of disagreeable odor, so that they have not been used as narcotics. **Paraldehyde** ($C_6H_{12}O_3$), a polymer of ordinary aldehyde, is, however, one of the newer hypnotics. Several derivatives of the aldehydes have been introduced, such as **Methylal** ($HCH(OCH_3)_2$) and **Acetal** ($CH_3CH(OC_2H_5)_2$). Another important aldehyde derivative is **Sulphonal** ($(CH_3)_2C(SO_2C_2H_5)_2$), which has received considerable attention of late years as a hypnotic. Two analogous

Cl into a comp. tends to; i.e. ↑ narcotic [illegible] + much more toxic [illegible]

compounds, **Trional** and **Tetronal**, in the first of which one, in the second both methyl groups are replaced by ethyl, are said to be more powerful than sulphonal.

The only member of the *ketones* which has received attention at the hands of therapeutists, is **Hypnone** ($C_6H_5COCH_3$), which has been used as a hypnotic.

The *esters*, or *ethereal salts*, have been but little used as depressants, and seem to be much weaker in action than the corresponding ethers.[1] Some of them, as amyl nitrite, owe their use not to the action of the alkyl radicle, but to the acid with which it is compounded, and are therefore included in another group. One ester which has been used as a narcotic in therapeutics, and to a much greater extent in animal experiments, is **Urethane**, the ethyl ester of carbamic acid ($CO(NH_2)(OC_2H_5)$). Analogous compounds recently recommended as hypnotics are **Hedonal** ($CO(NH_2)(OC_5H_{11})$), the carbamic ester of tertiary amyl alcohol, **Veronal**, or diethylmalonylurea ($(C_2H_5)_2C(CONH)_2CO$), and **Neuronal**, or bromdiethylacetamide ($(C_2H_5)_2BrC{\cdot}CONH_2$).

The *acids* of the methane series possess little narcotic action as a general rule, and have not been used in therapeutics for this purpose, though butyric acid is said to have distinctly depressant effects on the central nervous system. When hydrogen atoms of these acids are replaced by chlorine or bromine, they acquire a much stronger action; thus acetic acid is practically devoid of narcotic action, while some of the chloracetic and bromacetic acids are narcotic. But their effects on the other organs of the body preclude their use in therapeutics.[2]

Some of the most important members of this series are *halogen-substitution products*, formed by replacing one or more atoms of hydrogen in the simpler substances of the fatty series by chlorine. This substitution often increases the narcotic power to a very great extent: methane (CH_4) is practically not depressant, but if one, two, or three of the hydrogen atoms in the molecule be substituted by chlorine, forming CH_3Cl, CH_2Cl_2, and $CHCl_3$, the narcotic power increases with each Cl added. The best known of these is **Chloroform** ($CHCl_3$), which is the most powerful anæsthetic in use. The analogous compounds, **Ethylene Chloride** ($CH_2Cl - CH_2Cl$) and **Ethylidine Chloride** ($CH_3 - CHCl_2$), have fallen into disuse, but ethyl chloride (C_2H_5Cl) has recently been recommended for short operations. Another important substitution product is **Chloral**, or chloral hydrate ($CCl_3CH(OH)_2$), which is the hydrate of trichloraldehyde (CCl_3CHO). An analogous compound is **Butyl chloral**, or **Croton chloral** ($C_3H_4Cl_3CH(OH)_2$). **Chloretone** or **Aneson** (trichlorpseudobutylalcohol, $CCl_3C(CH_3)_2OH$) and **Isopral** (trichlorisopropylalcohol, $CCl_3CHOHCH_3$) have recently been recommended as hypnotics.

Several compounds of chloral have been introduced into therapeutics, such as **Chloralamide** ($CCl_3CHOH - NHCHO$), which is a combination of chloral with formamide, and **Chloralose** ($C_8H_{11}Cl_3O_6$), a compound of chloral and grape sugar.

It has already been mentioned that the substitution of chlorine for hydrogen in the acids endows them with a narcotic effect. Another example of the alteration of the properties of a substance by the substitution of chlorine for hydrogen is offered by glycerine, which in itself inert, becomes depressant to the central nervous system when its hydroxyl radicles are replaced by chlorine.[3]

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[1] *Vogel*, Pflüger's Arch., lxvii., p. 141.

[2] *Mayer*, Arch. f. exp. Path. u. Pharm., xxi., pp. 97, 119. *Pohl*, ibid., xxiv., p. 142.

[3] *Marshall* and *Heath*, Journ. of Physiol., xxii., p. 38, and *Kionka*, Arch. internat. de Pharmacodyn., vii., p. 475, give a résumé of the relation of the chlorine substitutes to the simple methane derivatives.

1 imperfect consciousness confused ideas
2 wild excitement—inhibitory faculties depressed.
3 complete unconsciousness
4 [illegible] death

Some attempt has been made to introduce bromine instead of chlorine into the methane derivatives, because bromides are central nervous depressants, and it was hoped that a combination of the methane and the bromide effects could be thus obtained. But, as will be explained, the bromides owe their action to the bromide ion, which is not present in these organic compounds. **Ethyl bromide** (C_2H_5Br) has been used as an anæsthetic, and **Bromoform** ($CHBr_3$) as a narcotic, but only to a limited extent. The analogous compounds formed with iodine possess a powerful action which is different from that of the other methane derivatives, and which precludes their use as narcotics. (See Iodoform.)

The augmented effect of these halogen substitution derivatives has been explained by reference to a supposed depressant effect of chlorine and bromine upon the brain. But even though this were proved to be the case, it would not elucidate the matter, for chlorine is not set at liberty in the tissues when chloroform is inhaled, the molecule acting as a whole.

The chlorine and bromine derivatives of methane are not only more powerful drugs, but also more powerful poisons than the ordinary compounds: much less chloroform is required to anæsthetize than methane, but much less is required to kill. In addition, these compounds, especially those containing chlorine, seem to have a more powerful action on the heart and circulation and on the metabolism than the others. In other words, the chlorine bodies have a wider field of activity and are more nearly general protoplasm poisons. (See Chloroform.)

Many methane compounds are not narcotic because they contain more active radicles. Thus ethane (C_2H_6) is a member of the narcotic series, but ethyl nitrite ($C_2H_5O - NO$) cannot be classed with it, because the $- O - NO$ group has a very powerful and entirely different effect; very small quantities of ethyl nitrite are required to produce the nitrite effect, so that the depressant action is pushed into the background. Members of the methane series often lose their depressant action when combined with nitrogen so as to form substituted ammonia. Thus trimethylamine ($N(CH_3)_3$) has no depressant action, although each of the methyl radicles alone would possess it. Again, the substitution of a member of the aromatic series for one of the fatty substances sometimes changes the action from that characteristic of the alcohol-chloroform group to that of the benzol series. For example, ether ($C_2H_5 - O - C_2H_5$) is one of the most valuable anæsthetics, but if one ethyl radicle be substituted by phenyl ($C_6H_5 - O - C_2H_5$), it loses this property entirely. Others, however, retain their depressant action, as, for example, acetophenone ($C_6H_5 - CO - CH_3$).

All of the narcotics of the methane series resemble each other closely in their general action. This consists of a first stage of imperfect consciousness and confused ideas, followed by one of wild excitement, and eventually by complete unconsciousness, which may terminate in death. The second stage is much more marked after some of the series than after others, and is often entirely absent. It has given rise to the theory that these drugs stimulate the nerve cells before paralyzing them, but an alternative explanation is that the functions of control and inhibition are lessened, and the centres of motion are thus left free and act more strongly than normally. This question has been most discussed in regard to alcohol, and will receive greater attention under that heading.

The depression of the central nervous system induced by these bodies is in the majority of cases accompanied by an alteration of the circulation of the brain in the direction of congestion or anæmia, and

Depression of CNS. cells leads to congestion + anaemia as in sleep

it was formerly believed that these drugs induced depression by causing anæmia of the brain and thus starving the nerve cells. But this improbable explanation has been refuted by experiments in which all the blood of a frog was replaced by salt solution, and the brain cells thus deprived of nutrition before an anæsthetic was applied; chloroform then induced the same changes as in normal animals. There is no question at the present time that these bodies act directly on the neurons and some evidence exists that the synapses between the cells, and not the cells themselves, are the primary site of the changes. Many suggestions have been made as to the nature of these; for example, coagulation of the proteins, solution of the lipoids, or changes in the chromatin and dendrites, have all been put forward, but no definite evidence of histological change has been adduced. There is every probability that the nerve cell depressed by drugs undergoes changes similar to those of natural sleep and the alterations in the brain circulation (anæmia) are the result and not the cause of the depression in both conditions.

While the members of this group resemble each other closely in their effects on the central nervous system, they are used for very different purposes in therapeutics and may therefore be discussed in three subgroups: 1, alcohol; 2, general anæsthetics, and 3, narcotics or hypnotics. It must be recognized, however, that there is no hard and fast line dividing these subgroups; for the anæsthetics, chloroform and ether may be used in small quantities to produce rest and sleep, and would then, strictly speaking, be narcotics; while, on the other hand, chloral and sulphonal, which are generally used as hypnotics, give rise to complete anæsthesia when administered in large quantities.

1. Alcohol.

Ethyl alcohol (CH_3CH_2OH) has been known in an impure form since the earliest times, and as far back as the history of medicine extends, has been used as a drug. Its medicinal reputation has undergone many fluctuations, by many held to be a panacea, by others it has been considered of little or no value as a remedy, but of the greatest importance as a poison.

Alcoholic liquors are generally prepared by the fermentation of sugars, which either exist preformed in the fruits, or are derived from starch by a preliminary ferment action. The simple liquors (wines and beers) generally contain only a low percentage of alcohol (2–20 per cent.), and the stronger preparations (spirits) are prepared from them by distillation, which raises the percentage to 30–60 per cent. and at the same time removes the non-volatile constituents. Spirits and liquors are not, however, simple mixtures of alcohol and water but contain many other volatile substances, the character of which is little known, and which are called œnanthic ethers. Some of them have been shown to be higher members of the alcoholic series, while others would seem to be of entirely different constitution. The name is derived from their giving the odor and taste, or bouquet, to wines.

Uses in medicine: 1) local irrit. Partial ppt. proteins. Redness 60-90%. 40-50% = evaporates = cold. Irrit. of [illegible] & promotes [illegible] of [illegible]. Burning on mucous mem.
3) As a food. 2) Loss of self control - excitement followed by slumber.

Pure alcohol is obtained from these spirits by repeated distillation and by special measures designed to remove the water. It is seldom used in medicine, some form of spirits, wine, or beer being prescribed instead.

Action.—The value of alcohol in medicine depends upon three chief points: 1, its irritant local action; 2, its action on the central nervous system, and 3, its value as a food.

The **irritant action** is not so marked as that of many other substances, but is of much great importance, owing to the habitual use of this drug. It is probably due to the partial precipitation of the proteins of the cells and is shown by the results of its application to the skin, to wounds and to the mucous membranes. Applied to the skin in sufficient concentration (*e. g.,* 60–90 per cent.), it produces redness, itching and a feeling of heat like other volatile and irritant substances, such as the volatile oils. Alcohol is, however, much less irritant and at the same time more volatile than these, so that unless its evaporation be prevented, it may produce a sensation of cold and have little or no irritant action; this is especially the case when dilute alcohol is used, no very distinct appearances of irritation of the skin being produced by solutions under 40–50 per cent. In ulcers and other unprotected surfaces, the irritant action is much greater and the cell division is accelerated, so that, judiciously applied, it may quicken the healing of such breaches of continuity. Concentrated solutions, however, cause a precipitation of the proteins, and act first as astringents and later as corrosives, until they are diluted by the fluids of the wound.

Its effects on mucous membranes are similar to those on wounds. In the mouth strong alcohol produces a burning, unpleasant sensation which passes to the throat and stomach when it is swallowed, and if the concentrated vapor be inhaled, it causes irritation and reflex closure of the glottis. The effects of alcohol on the digestive functions are so important that they will receive further attention (p. 139).

The action of alcohol on the **Nervous Centres,** differs a good deal in individuals. In small quantities it generally produces a feeling of well-being and good-fellowship, along with increased confidence in the powers, mental and physical, of the subject of the experiment. Larger quantities are followed by a certain amount of excitement, marked by laughter, loquacity and gesticulation. The face becomes flushed and hot, the eyes brighter and livelier, the pulse is accelerated. Even at this stage self-control is partially lost and the will power is weakened. The speech may be brilliant, but it often betrays the speaker; the movements are more lively, but they are often undignified. The loss of self-control is often indicated further by furious outbursts of anger and unreasonableness, or by the indulgence in maudlin sentimentality and sensual fancies. The sense of responsibility and the power of discrimination between the trivial and the important are lost, and the individual has no regard for the feelings of others or the ordinary conventions of life. If the bout be further continued, the

Nausea & vomiting often. Depression on waking – loss of appetite, vomiting. May lead to un., even cessation of resp. Excitement is a depression of higher will & self-restraint.

movements become uncertain, the speech becomes difficult and stammering, the walk becomes a stagger, and a torpid slumber follows. Often nausea and vomiting set in, although these are entirely absent in some cases. On awaking from slumber, very great depression is generally suffered from, together with nausea and vomiting, and want of appetite, which may last for several days and is associated with all the symptoms of acute gastric catarrh.

Very large quantities of alcohol lead to a deep, torpid sleep, which eventually passes into total unconsciousness, resembling the condition in chloroform anæsthesia; the respiration becomes stertorous and slow, and the face, which has hitherto been flushed, becomes pale or cyanotic. This condition may last for several hours and end in death from failure of the respiration, but in other cases the anæsthesia becomes less deep and after a very prolonged sleep the patient recovers. When the stage of anæsthesia is reached, it lasts very much longer than that produced by chloroform and ether. It is said that persons rarely or never recover if unconsciousness lasts longer than 10–12 hours after the drinking bout.

The effects of alcohol vary greatly, however, in different individuals and in the same individual at different times. One person is rendered sentimental, another bellicose, while in a third there may be no appearance of excitement, the first distinct symptom being profound slumber. When drinking is indulged in in company, the excitement stage is a very common phenomenon, but if alcohol is taken without the exhilarating accompaniments of bright lights and exciting companionship, it is much less frequently seen, and the question has therefore arisen how far the environment produces the excitement in alcoholic intoxication.

It may be stated at once that there exist two distinct views as to the action of alcohol on the central nervous system: the one stoutly upheld by Binz and his pupils, that alcohol first stimulates and then depresses the nerve cells; the other championed by Schmiedeberg, Bunge and their followers, that it depresses the central nervous system from the beginning. The symptoms of excitement require no explanation on the first theory, which is rather to be looked on as the natural expression of the facts observed. On the other hand, Schmiedeberg explains them as not due to true stimulation of the motor areas, but as the result of these areas being freed from control by the weakening of the highest functions of the brain—the will and self-restraint. Even the smallest quantities of alcohol tend to lessen the activity of the brain, the drug appearing to act most strongly, and therefore in the smallest quantities, on the most recently acquired faculties, to annihilate those qualities that have been built up through education and experience, the power of self-control and the sense of responsibility.

The question is a most difficult one to decide, for on the one hand it has been shown that the simplest movement is the result of a combination of motor and inhibitory impulses from the brain, while on the other hand the measurement of the relative strength of these impulses

rilliant after dinner speech – loss of shyness etc., not mental stimulation.
roops march better without alcohol (hence a depressant). Lessened muscular
fficiency is the rule.

is one of the most difficult problems of biology. The advocates of the stimulant action point to the confidence in their own powers exhibited by intoxicated persons, to the brilliancy of the after-dinner speech, and to the excitement stage as evidences of the increased activity of the brain. But their opponents question whether the confidence is accompanied by any really increased physical strength, and point out that the brilliancy of speech may be due to the environment and to the speaker having lost his habitual shyness and nervousness, and that the excitement is generally absent when the associations are different, or degenerates into a form which more distinctly resembles depression.

More definite evidence for or against the stimulant action of alcohol has therefore been sought by comparing the amount of work which can be done with and without it; and an apparent confirmation of Bunge's view has been found in the results of the use of alcohol by troops on the march, for repeated experience has shown that those regiments which were not supplied with alcohol marched farther and were in better condition at the end of the day than others to which it had been given. The experiments of Durig in climbing lead to the same result, the total work done being smaller under alcohol and the expenditure of energy greater. Forms of work requiring larger drafts upon the intelligence than the marching of soldiers are also performed less correctly with alcohol than without it; thus typesetters can do more work and make fewer errors when they abstain from its use. The capacity for work depends not so much upon the actual strength of the muscles as upon the condition of the brain, and these experiments are therefore generally quoted as evidence of the depressant action of alcohol. Their results are not incompatible with the view that alcohol primarily stimulates the nerve cells, however, for Binz and his followers allow that the stimulation is transient and is followed by depression, and if a sufficient time elapse after the alcohol is taken, the stage of depression is elicited and the total work may thus be reduced. A more exact method of examining the initial effects of alcohol on work is afforded by measuring at different intervals after the drug is given the work of which a muscle is capable before it is completely fatigued. This has been done in a number of experiments with the ergograph and the dynamometer, but the problem has not proved so simple as it appeared and the observers have obtained very divergent results. The careful and elaborate investigations of Rivers indicate that small quantities of alcohol (5–20 c.c., corresponding to about a tablespoonful and a wineglassful of spirits) have very little effect on muscular work measured in this way. Most observers agree that larger quantities diminish muscular work, and the statement that small quantities facilitate it seems to be based on experiments in which the errors of suggestion were not sufficiently appreciated.

The measurement of intellectual work is, of course, much more difficult, and the results are very liable to misinterpretation, but Kraepelin found in a series of careful measurements of the simpler

Intellectual powers accuracy. memory depressed — even with moderate amts dont recover for 12–24 hrs. Can better judge weights. Pain sense lessened. In acute intox — cells changed — granules replace chromatin.

cerebral processes that the receptive and intellectual powers were weakened by very small quantities of alcohol, while the motor functions seemed to be facilitated by small, and retarded by large quantities. For example, a person under even a small dose of alcohol makes more errors than usual in adding a row of figures and in reading a series of unconnected syllables, and apparently recognizes letters and words somewhat more slowly. It is interesting to find that the subject of the experiment is quite unaware of the inferiority of his work and is often persuaded that it is unusually good. It must be added that this depressant effect is not equally readily elicited in different individuals and even 100 c.c. of alcohol (corresponding to about half a pint of spirits) fails to induce it in some persons. Kraepelin's latest investigations tend to show that this effect of alcohol lasts much longer than is generally recognized, the mental equilibrium being reinstated only 12–24 hours after even very moderate indulgence in alcohol. He leans to the view that alcohol weakens and paralyzes some parts of the brain, while primarily stimulating others, but brings forward no new evidence that this stimulation is not fictitious and really due to the removal of the barriers of self-restraint by the paralysis of higher areas. Jacoby found that small differences in weight could be estimated more correctly under alcohol than in the normal condition of the brain, and this would seem at first sight to indicate primary stimulation, but he believes that the true explanation is a retardation of the cerebral processes. The sensation of pain is also found to be lessened by even small quantities of alcohol. No unequivocal evidence of the initial stimulant action on the brain has yet been adduced, for each new feature may be interpreted as really due to the depression of controlling or inhibitory functions. Of course, there is no absolutely convincing proof that no stimulation of the motor areas occurs, and no physiological proof of the existence even of controlling areas can be adduced, much less of their paralysis by alcohol. On the other hand, the effects of alcohol on cerebral activity are very different from those of caffeine, which definitely increases both muscular and mental efficiency, and thus is the typical brain stimulant. Exaggerated importance has been attached to this question from the idea that it is more justifiable to employ a "stimulant" than a "depressant," but in therapeutics this is not a valid argument for or against the use of alcohol.

Acute alcoholic intoxication leads to very distinct alterations in the histological appearance of the cells of the central nervous system, which have been described by Dehio, Stewart and others. The chief change noted by them consists in replacement of the chromatin network by fine granules, which in turn seem to become dissolved in the general cytoplasm. Staining reagents, therefore, give rise to a diffused coloration of the cell rather than to localized masses of color, such as are seen in the normal cell. The dendrites are shortened and exhibit rounded nodosities along their course.

In the lower parts of the central nervous system the evidences of primary depression are less open to question. For example, the coör-

Cord may be paralyzed after resp cessation -

dination of the movements suffers at an early stage in alcohol drinking, long before the generally recognized forms of lack of coördination, such as indistinct speech and staggering, appear. In the spinal cord alcohol causes a depression of the reflex irritability, which passes into complete paralysis some time before the respiration ceases.

The medulla oblongata is the last part of the central nervous system to be acted on by alcohol, or at any rate to undergo complete paralysis. The **Respiratory and Circulatory Centres** preserve their functions long after the occurrence of complete unconsciousness and the disappearance of the ordinary reflexes. The same question has been raised in regard to the respiratory centre, as has been already discussed in the consideration of the brain, and the same two opposing views have been upheld. These are of greater importance as regards the respiratory centre, because the advocates of the stimulation theory advise the use of alcohol in conditions of the respiration in which it is directly contraindicated if the other view be the correct one. The question here is apparently much more simple, because the activity of the respiratory centre can be estimated directly by measuring the number of the respirations and the amount of air inhaled during each; but a large number of such experiments have been performed with very varying results. If the number of the respirations be counted in a person in the excitement stage of alcoholic intoxication, it is often found to be much greater than normally, but this may be due to the muscular movements and need not indicate any direct action of the drug on the medullary centre. And, of course, this excitement stage is not elicited in therapeutics, and the value of alcohol as a respiratory stimulant must therefore be estimated in cases in which no such excitement is caused. A number of such estimations have been made in man and animals, and on the whole the evidence shows that in man even when no excitement is produced and in some instances even when sleep follows, the amount of air inhaled is larger than before the drug was administered (Jaksch, Zuntz and Berdez, Geppert, Weissenfeld, Wendelstadt); the increase is generally more evident when alcohol is taken during fatigue and exhaustion than in ordinary conditions. This may not indicate a direct stimulation of the respiratory centre, however, for the increase is often not greater than that following an ordinary meal, and may therefore be attributed to the respiratory centre being indirectly affected by the activity of the stomach and intestine. And it is to be noted that alcohol may have more indirect effect on the respiration than ordinary food because it is so much more irritant to the stomach wall. These experiments failing to determine whether the respiratory centre is directly stimulated in man, another method has been employed by Loewy in which the excitability of the centre was estimated by its response to the stimulus of an increase of the carbonic acid in the blood. Unfortunately, his experiments were too few to permit of general inferences, but they lend no support to the theory that the irritability of the centre is increased. There is therefore no sufficient evidence that the respiratory centre is directly stimu-

Resp up (exclusive of II) - not a stimulation of but reflex from peripheral action in g.i. (depression not until late in n.s.). By narcotic property may slow resp in fever & raise it in shock (lessening activity of inhib centres). Resp changes under any cond very slight. B.P. slightly up. Heart beats stronger due to nutritive effect on heart - not to a specific stim. In conc. sol for long time = effects as ether (but 200 × weaker) - fall in b.p. (but not direct)

lated in man, and the increase in the amount of air inhaled may be due to the peripheral action of alcohol.

In the dog, no acceleration of the respiration occurs after alcohol, while in the rabbit, on the other hand, the respiration is much accelerated, and the amount of air inhaled shows a corresponding increase. Jacquet has attempted to show that this is due to the local action of the alcohol, and not to any direct effect on the nervous system, but his results have been disputed by Wilmanns; Singer also refuses to recognize the changes in the rabbit's respiration as an indication of direct action on the respiratory centre, and is disposed to attribute them to the irritation of the stomach and the increased muscular activity, which is rendered necessary by the loss of heat entailed by the dilatation of the cutaneous blood vessels.

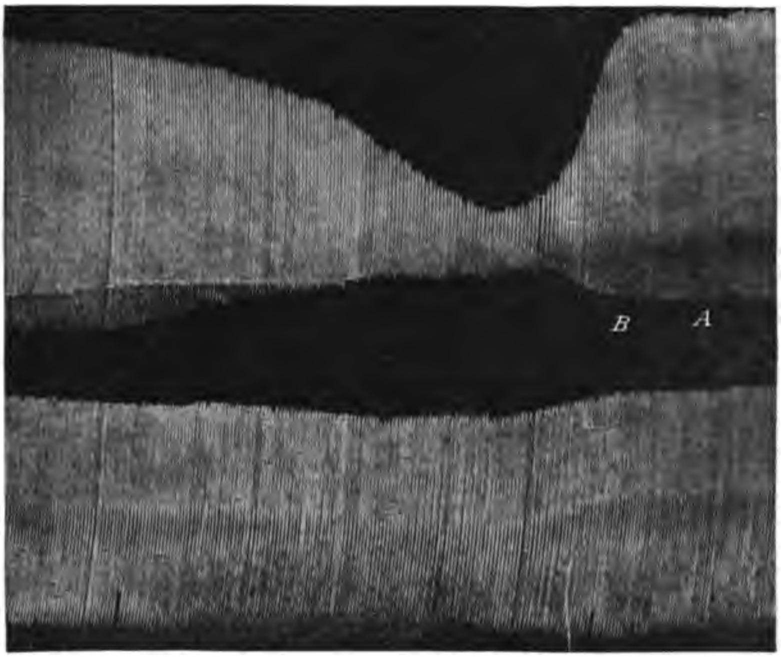
In short, there is no unequivocal evidence that the increase in the respiration under alcohol in health is due to direct stimulation of the respiratory centre, while on the other hand, no depression of the activity of this centre occurs except at a late stage of alcohol poisoning. Alcohol is often said to slow the respiration in fever patients and to stimulate it in cases of shock. In the first case, however, there need be no direct action on the respiratory centre, for it seems much more likely that the improvement (when present at all) is due to the alcohol lessening the excitement through its narcotic action. The pathology of shock is so little understood that it would be useless to attempt to explain its therapeutics, but if, as is held by many, shock is a condition of great inhibitory activity, the action of alcohol may be explained by its depressant effects, while on the other hand, it is difficult to explain these two contradictory effects on the theory that alcohol is a stimulant of the respiratory centre.

From a practical point of view the question is of little importance, for the changes in the respiration induced by alcohol are too small and too inconstant to play any part in the treatment of respiratory disorders.

Circulation.—The pulse is accelerated during the excitement of alcoholic intoxication, but this is due to the increased muscular effort and not to any direct action on the heart, for Jacquet has shown that the pulse rate is unaltered by alcohol in ~~normal cases, provided that no~~ excitement be produced by the environment. In animals also, the pulse rate is very little altered by alcohol except in very large quantities, when it is slowed. A small and inconstant rise in the blood-pressure is stated to occur in man under moderate quantities of alcohol (15–30 c.c.), and in animals a slight rise in the blood-pressure has been experimentally elicited in some cases, though it does not seem to be constant. This increase has been attributed to alcohol augmenting the strength of the heart, and in experiments in which the excised mammalian heart is kept in activity by perfusion with Ringer's solution, the addition of a small amount of alcohol (1 per mille) to the perfusing fluid often strengthens the contraction. Dixon suggests that this is not a true stimulating action, but is due to the alcohol serving as a source of energy in the same way as sugar. This strengthening action is observed only under very dilute alcohol, and larger quantities affect the heart in the same way as ether and chloroform, weakening the auricular and later the ventricular systole, and inducing dilatation and slowing of both chambers (Fig. 3). The action of alcohol on the heart is much less than that of chloroform, however, about 200 times as much being required to arrest the frog's heart; and Loeb found that the mammalian heart continues to beat when perfused with 2 per cent. alcohol.

The flushing of the skin which occurs in alcoholic intoxication indicates dilation of the skin vessels, and this is sometimes accompanied by a very slight constriction of the vessels of the internal organs.

FIG. 3.



Tracing of the movements of the ventricle (lower) and auricle (upper) of the dog when a large dose (20 c.c. or 2/3 oz.) of 50 per cent. alcohol is suddenly thrown into a vein. The levers move upwards during systole, downwards during diastole. *A*, normal. *B*, injection. The systole of the auricle is very much weakened, the diastole is less affected. The ventricular systole is comparatively little changed, although it also is a little weaker. The effect passes off very rapidly, so that at the end of the tracing both chambers have almost recovered. A very similar effect is seen under chloroform. (Fig. 10.) (The tracing is to be followed from right to left.)

These seem to arise from central vasomotor action, but whether it is due to direct stimulation of the centres or arises from a reflex from the periphery is not yet determined. Very large quantities of alcohol cause a marked fall in the arterial tension, through weakening the vaso-constrictor centres and the heart muscle, but the quantities of alcohol required to cause any great fall in blood-pressure are far in excess of those used in therapeutics.

On the whole, the action on the circulation of small quantities of alcohol ($\frac{1}{2}$–1 oz.) may be favorable in some conditions, by augmenting the strength of the contraction of the heart, but this action is so slight

Action on circ. variable & negligible in therapeutics: Possibly slows heart in fever & better in shock. Muscle uses alc. as food; Nerve = depression. Digestive ferments not more active. Large quantities ppt the proteins, unless very rapidly absorbed. Locally in mouth & stomach = increases secretion due to irrit.

and inconstant that it is impossible to regard it as a basis on which serious therapeutics can be founded.

The slowing of the heart which often follows the administration of alcohol in fever, would seem due rather to its diminishing the cerebral excitement than to its direct action on the heart. On the other hand, the alleged improvement of the circulation in shock may be due to a reflex from the irritant local action, and perhaps to the direct cardiac action.

Alcohol has little effect on **Muscle** or on peripheral **Nerves** when it is carried to them by the blood, but Lee states that frog's muscle is strengthened by small quantities and weakened by larger amounts. This has been interpreted as indicating that small quantities of alcohol are utilized by the muscle as a source of energy, while this effect disappears under larger quantities which unfold the toxic action of the drug. And Durig's experiments show that in man alcohol may be utilized for work in the same way as the ordinary sources of energy such as sugar. When the frog's nerve is exposed to alcoholic vapor its irritability is first increased and later diminished if the quantity applied be large enough. The sensory fibres are said to be depressed before the motor.

The effect of alcohol on the **Digestion** has been the subject of many investigations, both from the clinical and the experimental point of view. There exists a widespread belief in both lay and medical circles that small quantities of alcohol taken before a meal increase the appetite, while after food they accelerate the digestion. It is obvious that alcohol may affect digestion either by altering the activity of the ferments in the digestive canal, or by altering the secretion, movement, or absorption of the stomach and intestine. The digestive power of the *ferments* outside the body has been found to be unaltered or slightly increased when alcohol is present in very small quantity. In a solution of 5–10 per cent. of alcohol or of spirits, however, the gastric juice digests very much more slowly than normally, and the pancreatic secretion is affected prejudicially by even smaller quantities. (Chittenden and Mendel.) Very large quantities of alcohol precipitate the proteins, but it is unlikely that sufficient alcohol to produce this effect ever remains in the stomach for any length of time. The malt liquors and wines are much more detrimental to the digestive ferments than pure alcohol or spirits, and the augmentation of the activity of the ferments is so slight in any case that it does not seem likely that it plays any important rôle in the effects of alcohol on the stomach.

The presence of alcohol in the mouth causes (according to Chittenden, Mendel and Jackson) a very appreciable increase in the secretion of the saliva, presumably by reflex action. As regards the action on the *stomach wall,* it is to be remembered that alcohol, even in comparatively dilute solution, is an irritant, and therefore leads to increased activity of the cells, a more active circulation in the organ, and probably to a more rapid secretion of both acid and solids of the gastric juice. But apart from this local action on the stomach, it appears to

reatly increases absorption of substances & movements of stomach increased.
ine, beer, spirits = deleterious action on ferments but beneficial + increased secretion
if individual likes taste. May balance & do harm or good. In large doses always harm,
ucus & vomit – local irritation.

exert a specific action on the secretion after its absorption into the circulation. For when it is injected into the dog's rectum, a profuse secretion from the gastric mucous membrane follows, and when part of the stomach is isolated from the rest of the organ, so that alcohol given by the mouth fails to enter it, this part still shares in the secretion. According to Radzikowski, the pepsin secretion is not always correspondingly augmented, the alcohol not accelerating the formation of pepsin from propepsin, but merely leading to the secretion of the pepsin preformed in the cells. Similar effects have been obtained in man by Spiro, who administered alcohol by the rectum. It has been further demonstrated that the absorption of fluids from the stomach and bowel is much accelerated by the addition of alcohol (Brandl, Scanzoni, Farnsteiner, Tappeiner), and the movements of the stomach are also augmented by moderate quantities. (Klemperer, Batelli.)

Digestion in the stomach may thus be influenced in two opposite directions when alcohol is administered in the usual form of wine, spirits, or beer. The action on the ferments is deleterious, while the changes in the stomach wall, the increased secretion and movement and the accelerated absorption, are beneficial in many cases. These two opposing factors may neutralize each other, as in the dog in which the rate of digestion is scarcely altered, the retarding effects of alcohol on the proteolysis being compensated for by the more abundant secretion of the juice, which continues after the alcohol is absorbed, and therefore after its deleterious effects on the fermentation have disappeared. (Chittenden, Mendel and Jackson.) In man the result varies, the one factor predominating in some cases, the other in others. Thus, while Kretschy and Buchner found that the digestion of proteins in the human stomach was distinctly retarded by alcohol and beer, Eichenberg, Wolffhardt and others state that small quantities of alcohol or wine accelerate the digestion, and Gluzinsky came to the conclusion that as long as alcohol remains in the stomach the digestion is retarded, but that after its absorption the digestion progresses more rapidly than if no alcohol had been given. Zuntz and Magnus-Levy have shown that the addition of beer to the dietary does not affect the absorption and utilization of the food by the tissues. It is not unlikely that the taste has some influence on the result, that in those who enjoy the taste of alcohol, it induces a more rapid secretion and an improved digestion, while in those to whom it is disagreeable the secretion is less altered.

The divergence of opinion exists only in regard to the effects of small quantities, for all are agreed as to the deleterious action of any but moderate doses of alcohol on the digestion. After large quantities (50 c.c.) the irritation of the stomach wall leads to a profuse secretion of mucus, nausea and vomiting. There is every reason to suppose that this is due to the local irritation, and not to the action of the absorbed alcohol on the nervous centres. A large dose of concentrated alcohol sometimes leaves evidence of its irritant action in redness and injection of the mucous membrane, and, it is said, in ecchy-

Only 5% excreted. 95% combusted yielding energy. It acts as substitute to
some extent for ch. & fats. Hence obesity. In vivo. diff probably from in vitro.
alcohol → acetic → combusted. No CH_2O as would be in breath. Alcohol
remains in blood 12–24 hrs – hence nervous effects.

moses, but in most cases of fatal poisoning no such appearances are to be observed after death.

Is Alcohol a Food?—This has long been discussed, and that with more passion and prejudice than are generally elicited by pharmacological questions. It has been shown that only 5 per cent. or less of the ingested alcohol is excreted, while the rest of that absorbed from the stomach and bowel, amounting to over 95 per cent., undergoes combustion. The fact that none of the products of the combustion have been isolated from the body does not invalidate this statement, for the corresponding products of sugar are not known, but there is no doubt that sugar is oxidized in the body.[1] According to Grehant's recent work, the oxidation of alcohol progresses slowly, appreciable amounts being found in the blood twenty-four hours after its ingestion; this accords with Kraepelin's statement that its effect on the brain can be detected for 12–24 hours. In undergoing combustion alcohol gives up energy to the body, and therefore is technically a food. This statement has met with a great deal of opposition, and the mere fact that alcohol gives up energy to the body does not constitute it an advisable food in all conditions. For example, the question might be raised whether alcohol does not require an amount of energy for its absorption equal to that liberated by its combustion, or whether its action on the nervous centres does not produce a greater waste of force than the food itself supplies. Both of these have been answered by experiments in which the carbonic acid excretion of the body has been measured before and after alcohol. Zuntz and Berdez and Geppert have shown by this method that after alcohol is taken, a slight rise of 5–10 per cent. occurs in the output of carbonic acid; that is, a small amount of extra combustion goes on, a certain amount of energy is required for the absorption, but this is not greater than that required for the absorption of any other form of food. And the total amount of carbonic acid excreted in 24 hours is not appreciably altered by alcohol, so that alcohol taken in addition to the ordinary food is either itself transformed into tissue, or undergoes oxidation instead of some substance which in turn is used to build up the body. Strassmann has shown that animals that receive alcohol tend to lay on more fat than others receiving the same food without alcohol, and this is in accord with the common observation of the obesity of alcohol drinkers. Alcohol, therefore, acts as a substitute for fats and carbohydrates in the food to some extent.

It has long been recognized that when insufficient fat and carbohydrate is supplied to the body, the proteins are drawn upon to make good the deficiency and the nitrogen eliminated rises accordingly. On the other hand, when the fats and carbohydrates of the food are increased, the organism economizes its protein and the nitrogen tends to fall. This is the most accurate method of testing the food value of non-nitrogenous substances, and alcohol has been the subject of a number of such investigations. The divergent results have given rise in the last few years to a series of experiments which promise to become classical for the extraordinary patience and conscientiousness exhibited by those engaged in them, as well as for the complete agreement in the results obtained by investigators who approached the subject with opinions which were diametrically opposed. These experiments, which may be cited as models of investigations in metabolism, were performed by Neumann, Atwater and Benedict, and Rosemann and his pupils. The results may best be illustrated by an account of Neumann's first experiment.

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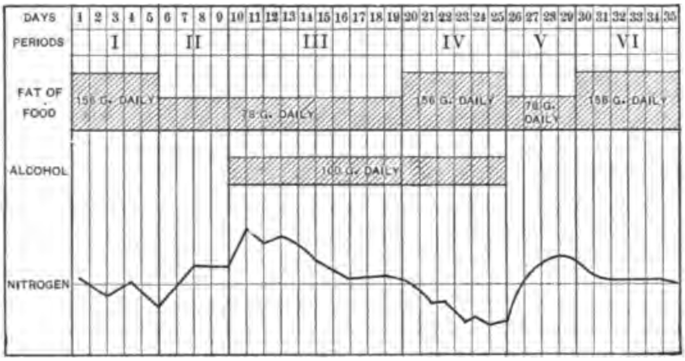
[1] It has been suggested that the oxidation of alcohol in the body may not give rise to the same products as its oxidation in the chemical laboratory. If aldehyde were formed it would be excreted in part by the lungs and kidneys, for aldehyde injected into the blood at once appears in the breath and urine. Acetic acid has never been identified with certainty after alcohol, but formic acid is excreted after methyl alcohol, and it therefore seems probable that ethyl alcohol is oxidized to acetic acid immediately, and that this at once undergoes further decomposition.

This lasted 35 days divided into six periods. The proteins of the food and the carbohydrates remained constant throughout, while alcohol was substituted for part of the fat for some time (see Fig. 4). During the first five days the nitrogen excreted was practically equal to that of the food (nitrogenous equilibrium), while during the next four days one half of the fat of the food was omitted and the immediate result was an increase in the nitrogen excreted, indicating that the proteins of the body were being drawn upon to make good the deficit in the fat of the food. The next ten days a quantity of alcohol chemically equivalent to the fat deficit was taken and the nitrogen elimination slowly fell to the normal (equilibrium). In the first five days of this period, however, the nitrogen remained high, showing that alcohol did not at first replace the fats completely. In the fourth period of six days, the same amount of fat was given as at first, while the alcohol

FIG. 4.



The effect of alcohol on nitrogen elimination. The wave-line represents the nitrogen excreted. It rises rapidly in the second period when the fat of the food was reduced to one half, but soon falls in the third period where alcohol was substituted. 100 g. of alcohol is chemically equivalent to 78 g. of fat. (After NEUMANN.)

CH + fats combustion economizes N metabolism. Alcohol may be substituted for fat + N kept constant. Increase of alcohol + normal diet = still further saving of N catabolism. Acetone from fat in diabetes may thus be lessened.

was continued, and the nitrogen fell much below the amount ingested; *i. e.*, the alcohol again led to a saving of the proteids. Next, both alcohol and fat were omitted for four days and the proteid tissues were again drawn upon. Finally the original diet was resumed and the nitrogenous equilibrium was at once restored. From this experiment Neumann drew the conclusion that alcohol can replace a chemically equivalent amount of fat in the dietary, for otherwise the nitrogen would not have returned to the normal toward the end of the third period; and alcohol given along with a sufficient dietary leads to a further economy of the proteins just as additional fat would; otherwise the nitrogen would not have fallen below the point of equilibrium in the fourth period. Certain objections which were made to this experiment by Rosemann have been refuted by his own work and by Neumann's, so that both investigators are now in accord.

The final result of all these investigations is that alcohol can take the place of some of the fat in the food, and leads to the same economy of protein as the ordinary non-nitrogenous constituents of the dietary. The first three or four days during which alcohol is substituted for fat it has little or no tendency to economize the proteins, but this is true of other forms of food also, any sudden change in the non-nitrogenous food leading to a temporary increase in the nitrogen excreted, which persists until the tissues have become accustomed to the new dietary.

Metabolism.—It was formerly supposed that alcohol economized the body tissues in some ill-defined way, by means of a direct action on the protoplasm of the cells; as it was expressed, alcohol lessened the combustion of the tissues. There is no reason to suppose that alcohol in ordinary quantities has any action of this kind on the tissues, for, as has been mentioned, the oxidation of the tissues as measured by the oxygen absorbed and the carbonic acid exhaled is only affected as it is by any other food. When very large quantities of alcohol are taken, and depression and sleep follow, the combustion of the body is reduced, not through any action on the protoplasm generally, but through the muscular movements being lessened. In the same way, during the excitement stage, the carbonic acid exhaled is doubtless much increased, because more energy and more of the body tissues is used up in the violent movements. Of course, the oxidation of alcohol by the tissues saves fat from combustion, and it is possible that some bodies which would normally be oxidized in the organism may pass through it unchanged in the same way. On the other hand, the excessive fat-destruction in diabetes sometimes gives rise to the formation of acetone in large quantities, and the administration of alcohol may lessen this symptom, through the alcohol undergoing combustion instead of the fat. The influence of alcohol on the uric acid excretion seems to vary with the individual, for while no definite change has been observed in some cases, even when large quantities of alcohol were taken, Beebe found a distinct increase in the quantity excreted under moderate doses. He ascribes this result to alcohol disturbing the functions of the liver, and further evidence of this action has been found by Paton uric acid excretion increased, even with purin free diet: Alcoholics have low resistance to infections (leucocytes & little complement). Not so in treatment of infect fevers – no lowering of resistance. Small chronic doses in some way alter metabolism (more susceptible to methyl cyanide)

and Eason in the lower proportion of urea to the total nitrogen of the urine. This increase in the uric acid excretion is said to occur also under alcohol on a purine-free diet.

It has long been recognized clinically that persons addicted to the use of alcohol show less resistance in acute disease and in operations accompanied by shock than more temperate individuals, and in very intemperate cases the prognosis must be guarded in an attack which would ordinarily be accompanied with little danger. This has been confirmed by a number of experiments on animals which were subjected to treatment with alcohol and then inoculated with pathogenic germs (Laitinen). The results have invariably shown a greater susceptibility to infection and a greater mortality than in control animals which had received no alcohol. A similar effect was observed when toxines were injected instead of bacteria, and great difficulty was encountered in rendering animals immune to the diphtheria toxin if they had previously been treated with alcohol. Various explanations of this reduced resistance have been given, Rubin ascribing it to paucity or inactivity of the leucocytes, while Abbott and Bergey found a reduction in the hemolytic complement, which suggests that the susceptibility to infection may be due to the failure to form the specific complement to the bacterial toxin. It is often stated that alcohol given in the treatment of infectious diseases must have a similar deleterious effect on the resistance of the tissues, but this has not been shown to be the case.

These clinical and experimental results have raised the question whether the ordinary dietetic use of alcohol in even small quantities (15–30 c.c.) may not lead to impairment of the resistance to infectious disease, and much interest attaches to Laitinen's later work in which animals were treated with quantities of alcohol corresponding to those habitually used by temperate persons. The general result appears to be that the prolonged use of small quantities in animals (0.1 c.c. per kilo) may affect their susceptibility to disease, but the average mortality is scarcely greater than that of the controls to which no alcohol has been given.

A much more distinct effect from small doses of alcohol, such as correspond to temperate use in man, has been observed by Hunt, who finds that animals thus treated become more susceptible to the action of methyl cyanide. This poison acts in the tissues through being oxidized to hydrocyanic acid, and Hunt believes that the effect of the prolonged treatment with alcohol is to facilitate this oxidation, and that the reaction is evidence of an alteration of the metabolism of the body in this direction. The great importance of this observation lies in the fact that the modification of the metabolism which it demonstrates, arises from the prolonged use of quantities of alcohol which are too small to give rise to definite symptoms of intoxication. Apparently the alteration is associated with the development of tolerance for alcohol.

The Temperature of the body falls somewhat after the administra-

[illegible] vessels = [illegible] temp. Regulatory mech less sensitive so much reduction if into cold. Incr. in movements. 20% absorbed by stomach. 80% by small i. In 24 hrs 95% oxidized. Unchanged → urine & lungs ("no odor from ethyl. breath" is higher alcohols etc.) Tolerance here is increased power to rapidly oxidize, hence less agn for blood amts.

tion of alcohol, but this is not due to any diminution in the oxidation and in the heat formed, but to the greater output of heat from the dilation of the skin vessels. The fall in temperature is comparatively slight, seldom being more than ½–1° C., but it would seem that exposure to cold causes a greater fall in the temperature after alcohol than in normal conditions; this is perhaps due to the temperature-regulating mechanism being rendered less sensitive by alcohol.

The fall in temperature produced by alcohol is generally accompanied by a feeling of heat, and a thermometer applied to the skin may actually show a rise of several degrees, because more warm blood flows through the dilated vessels. If much excitement and movement follow the ingestion of alcohol, no fall in the temperature may result, the increased heat formed during the movement compensating for the increased output, and in some cases a rise of temperature occurs from the same cause. Very large quantities of alcohol may lead to a fall in temperature of 3–5° C., owing to the lessened movements during unconsciousness.

Absorption and Excretion.—Alcohol is absorbed rapidly, about 20 per cent. of that ingested being taken up in the stomach and 80 per cent. in the small intestine. It rapidly passes into the tissues from the blood and is slowly oxidized. Grehant's experiments indicate that the blood may contain as much as six parts per thousand and the animal recover, but more than this inevitably proves fatal. Traces remain in the blood for about 24 hours, but over 95 per cent. of that ingested is oxidized in that time. The alcohol which escapes combustion in the tissues is excreted by the kidneys unchanged,[1] and by the lungs.[2] Traces are sometimes found in the sweat and milk, but there is no foundation for the legend that children may be intoxicated, or acquire a taste for strong drink from the alcohol absorbed in the milk of a drunken mother or wet-nurse. The amount and quality of the milk are unaffected by the administration of alcohol (Rosemann). Brauer states that alcohol is eliminated in some quantity in the bile and is then reabsorbed in the intestine. This is more marked in the case of amyl alcohol than in that of ethyl alcohol, and the appearance of alcohol in the bile is accompanied by albumin, epithelial cells and casts of the finer bile ducts.

Repeated doses of alcohol produce **Tolerance**, which, although not so great as that acquired for morphine and nicotine, involves the prescription of double or triple doses, in persons addicted to drinking. This tolerance has been shown by Pringsheim to arise in part from the tissues acquiring an increased capacity to oxidize alcohol; and as oxidation begins almost as soon as absorption, a large quantity of alcohol taken by a habitual drinker may not lead to the accumulation

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[1] Some of the alcohol in the urine is combined with glycuronic acid in the rabbit, but not in man.

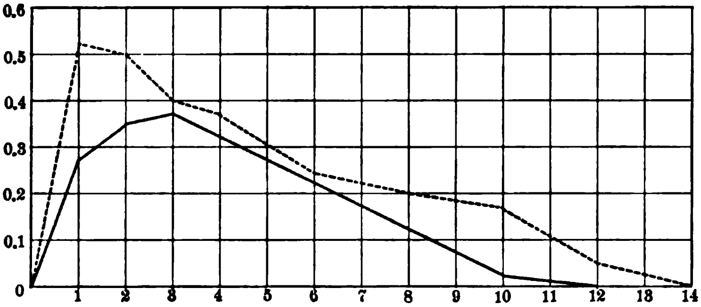
[2] Traces of alcohol are exhaled in the breath, but ethyl alcohol fails to escape in this way in measurable quantities. The odor of the breath after spirit drinking arises from the higher alcohols and other by-products present in these and not from the ethyl alcohol.

Cross tolerance — ether. Not an aphrodisiac: Shakespeare: the [illegible]
Weak antiseptic (only in 4%). Good disinfectant 50-70%. (moisture necessary) hence
absolute N.G. Some antiseptics N.G. when dissolved in alcohol.

in the blood of a sufficient quantity to induce symptoms of intoxication (Fig. 5). The close relationship between the narcotics of the fatty series is indicated by the fact that much more chloroform or ether than usual is required to anæsthetize persons in whom a tolerance for alcohol has been established.

Although alcohol seems to increase the **Urine** to some extent, it cannot be said to be a powerful diuretic in itself, and it is quite unknown whether it acts on the kidney directly or not. Some of the spirituous liquors, such as gin, produce a profuse secretion of urine, but this is due to their other constituents, and not to the alcohol.

FIG. 5.



The percentage of alcohol in the blood after giving 5 c.c. per kg. to rabbits. The percentage is indicated on the perpendicular line, the hours after administration along the horizontal. The broken line represents the changes in percentage in a normal animal, the unbroken that in an animal which had acquired tolerance through prolonged treatment with alcohol previously. (PRINGSHEIM.)

Alcohol is generally credited with **Aphrodisiac powers**, that is, with increasing sexual desire, although no less an authority than Shakespeare states that it prevents the consummation of sexual intercourse. The unquestionable tendency toward sexual excess observed in intoxication is due, not to any effects on the generative organs, but to the loss of self-control from the cerebral action of the poison.

Alcohol possesses only a weak **Antiseptic** action, for while the growth of some bacteria is delayed somewhat in a 1:1000 solution, many grow abundantly in 4 per cent. alcohol, and some in even stronger solutions. Its disinfectant action has been the subject of a number of researches recently and has been found to vary with the conditions. Dry bacteria may be exposed to absolute alcohol for twenty-four hours without losing their vitality, while 60–70 per cent. alcohol is fatal to them, and also to moist organisms. The explanation of this curious observation seems to be that alcohol fails to penetrate microbes unless in the presence of water. In less than 40 per cent. the action is very slow, so that the limits of alcohol as a disinfectant may be placed at 50–70 per cent.; in this strength it is equivalent to about 3 per cent. carbolic acid, provided that it does not cause large precipitates of protein. Many bodies which are antiseptic when dissolved in water have comparatively little effect when dissolved in alcohol.

Methyl alcohol — slower action — more gast. irrit. Very poisonous if repeated doses as = HCOOH + CH_2O = muscular weakness + poor cardiac weakness + optic neuritis + atrophy

Methyl alcohol, or wood alcohol, has assumed great importance lately from a large number of cases of poisoning having occurred from its being substituted for ethyl alcohol as an intoxicant, or in some patent remedies. In animal experiments it is found that given in single doses it is slightly less poisonous than ethyl alcohol, the action coming on somewhat more slowly, but lasting a longer time; the symptoms of gastric irritation are generally more marked than those induced by ethyl alcohol, and very often some convulsive movements are observed (Hunt). When the administration is repeated, methyl alcohol is found much more poisonous than ethyl, and this may probably be ascribed to the more prolonged action of the former. Pohl has pointed out that while ethyl alcohol undergoes complete combustion in the tissues, methyl alcohol is oxidized to formic acid and possibly formic aldehyde, both of which are much more poisonous than the original alcohol. It seems a fair inference that the prolonged action and the consequent greater toxicity of the lower alcohol may be due to these products.

In man the symptoms of wood alcohol poisoning differ from those of ordinary spirits in the marked muscular weakness and defective cardiac action, which are followed by nausea, vomiting, coma, or delirium of a much more intense and persistent character than those seen in intoxication with ethyl alcohol. In a considerable number of cases death has followed from a single dose smaller than would have been fatal had ethyl alcohol been swallowed, and in some cases total and permanent blindness has followed or accompanied recovery. This condition is more often the result of repeated ingestion of the alcohol, however, and is due to optic neuritis and subsequent complete optic atrophy. The large number of cases of blindness or fatal intoxication collected by Buller and Wood demonstrate clearly the danger incurred in the use of this poison internally or even externally. Optic atrophy has been induced in animals repeatedly by the administration of wood alcohol, and is certainly much less liable to occur from ethyl alcohol.

The **other alcohols** are mainly of interest as impurities of the preparations of ethyl alcohol. They all resemble it in their general effects, but differ from it in toxicity; propyl alcohol is more powerful than ethyl, butyl than propyl, and amyl than any of them. Amyl alcohol, or fusel oil, is present in small quantity in most forms of spirits. It resembles ethylic alcohol in general, but is more irritant locally, and is believed by some authorities to have more deleterious effects in chronic poisoning than pure ethylic alcohol. This is not based on any very satisfactory evidence, however, and all the characteristic symptoms of chronic alcoholism have been produced in animals by pure ethyl alcohol. Furfurol is also present in many forms of spirits, but in such small quantities that it does not play any rôle in the symptoms induced by them.

PREPARATIONS.

Alcohol (U. S. P.) contains 92% of alcohol (C_2H_5HO) by weight. 92%

Alcohol Absolutum (U. S. P., B. P.), absolute alcohol, contains not more than 1%, by weight, of water.

Alcohol Dilutum (U. S. P.) contains about 41%, by weight, of alcohol. 41%

Spiritus Rectificatus (B. P.), rectified spirit, contains 90 parts of pure alcohol, by volume, and 10 parts of water (85.65%, by weight, of alcohol). There are four official dilutions in the B. P., containing 70, 60, 45 and 20 per cent. of alcohol by volume respectively.

SPIRITUS FRUMENTI (U. S. P.), whiskey, contains 44–50% of alcohol by weight, and is obtained by distillation of an extract of fermented grain. 44-50%

SPIRITUS VINI GALLICI (U. S. P., B. P.), brandy, contains 39–47% of alcohol by weight, and is obtained by the distillation of fermented grape juice. 39-47%

Non-pharmacopœial spirits, which are used occasionally in medicine, are gin and rum.

Cherry water has [illegible]. Vinum album rubrum 7–12% Xericum 16%
Champagne 8–13% very "stimulating" much CO2 little alcohol.
Beers 4–10% – cho – may ferment – dextrin colloids prevent rapid absorption.
Hence beers porters have much nutrition if digestion undisturbed

These **Spirits** all contain, roughly speaking, about one half as much alcohol as the three concentrated alcohols of the U. S. P. or the rectified spirits of the B. P. They contain, in addition to the ethyl alcohol proper, numbers of other volatile substances, some of which are alcohols of the same series as ordinary alcohols (butylic, amylic, etc.), while others are of entirely unknown constitution—the œnanthic ethers. Brandy and whiskey act very much in the same way as pure alcohol. When freshly distilled they are more irritant and less pleasantly flavored than when kept for some years but do not seem more deleterious. Numerous other preparations containing large quantities of alcohol, such as the spirits of the volatile oils, might also be included in this group, but they are not used, as a general rule, for the same purposes as the alcoholic preparations proper, and their effects are in part due to the volatile oils contained. Some of them have, however, been employed as intoxicants instead of brandy or whiskey, and *Eau de Cologne* and other essences have gained a certain notoriety as a means of secret drinking among women. The liqueurs are too numerous to mention, and their composition is extremely diverse. Many of them contain considerable quantities of sugar, and the combination of alcohol and sugar would seem peculiarly deleterious to the gastric mucous membrane. Others, such as cherry water (Kirschwasser), contain hydrocyanic acid, and the others various bodies of the volatile oil series. None of them seem to have any properties which would recommend their use in therapeutics.

The **Wines** and **Beers** are much weaker preparations of alcohol. The U. S. P. recognizes two forms of wine, VINUM ALBUM (white wine) and VINUM RUBRUM (red wine, claret). These both contain 7–12% of alcohol by weight, along with 1.5–3% of solid matter in the white wine and 1.6–3.5% in the red. The VINUM XERICUM (sherry) of the B. P. contains not less than 16% of alcohol by volume, while the VINUM AURANTII (B. P.), or orange wine, contains 10–12% by volume. In addition, the wines contain the same volatile constituents as brandy, although in smaller amounts. Other wines are prescribed in medicine, some of which, such as port (15–20%), contain larger, and others smaller quantities of alcohol (hock and champagne 8–13%). The red wines contain a form of tannic acid derived from the skin of the grapes, and both red and white often contain considerable quantities of acids, chiefly tartaric acid. The amount of sugar varies with the different wines, and in fact in wine from the same locality but of different seasons. These constituents may lend to the wines a local deleterious action on the stomach, more especially when they are taken habitually. Champagne and the other sparkling wines contain large quantities of carbonic acid, which acts as a stimulant to the gastric mucous membranes. Champagne is considered one of the most "stimulant" of alcoholic preparations, although it contains a very low percentage of alcohol compared with spirits, a fact which is of some significance in the explanation of the "stimulant" effects of alcohol.

The beers are not pharmacopœial, and are less frequently advised than the other preparations. They generally contain a comparatively small percentage of alcohol (4–10%), along with a large amount of solids. These solids consist mainly of dextrin, sugar and other starch products, which retard the absorption of the fluid, but are of considerable value as foods. The hops added in the preparation have probably no action save as bitter stomachics. The alcohol of beer is comparatively slowly absorbed owing to the colloid dextrins, which may perhaps account for the discomfort produced by malt constituents, and this allows time for fermentation changes in the sugars and liquors in persons of feeble digestion. When beers and porter do not derange the digestion, they are the most nutritive of all the alcoholic preparations, owing to the large amount of carbohydrates they contain.

Threatening bedsores, ulcers – increases irritation. 50–70% [illegible]
If not evaporated 2 irritant action 1) local irrit 2) narcotic 3) food.
If absorption poor. good for gastric disturbances. If pleasant to patient = increase of
gastric secretion. Give just before meal.
In depression of heart use for shock hemorrhage, whiskey etc often given
but doubtful value unless local irrit reflexly excites centers' irritability.

Therapeutic Uses.—Alcohol is used *externally* in very dilute solution as a cooling application to the skin, and in threatening bedsores, in which it is often applied as brandy, whiskey, or dilute alcohol in order to harden the epidermis. It has been employed as an antiseptic and mild irritant to broken surfaces, and if applied to the skin in concentrated form, and especially if kept from evaporation, acts as a rubefacient and irritant. Its use to wash the skin and hands before operations arises from its power of cleansing the skin and removing the oils and fats rather than from its exercising any disinfectant action. In the form of diluted claret it is not infrequently used as an astringent gargle.

narcotic lower lessens anxiety.

The indications for the *internal* use of alcohol are ill defined, and cases which one physician would treat with alcohol often seem to progress as favorably without it in the hands of another. It is not sufficiently recognized that this drug possesses several different qualities, as local irritant, narcotic and food and that while one property considered alone might render it unadvisable in a given condition, the deleterious effect induced in this direction may be more than counterbalanced by its valuable results in other directions. At the same time it would be preferable in most cases to substitute for this conjunction of good and bad properties other drugs with a less extended sphere of action.

One series of symptoms which is often treated with wines is of gastric origin, and is manifested in want of appetite and enfeeblement of the digestion; in some of these cases the alcoholic preparations seem to be beneficial, while in others they appear to be positively harmful. This may be explained by the effect of alcohol on secretion and absorption, only those cases in which secretion is deficient being benefited, but the tastes of the patient are also an important factor; if he enjoys the taste and odor of wine, its administration may promote his appetite, while, on the other hand, if he has a distaste for wine, it will prove harmful. There is no question that the functions of the stomach are increased by pleasing, and retarded by unpleasant tastes and odors. In these cases "dry" wines are to be preferred, as the sugar of the sweet wines may irritate the stomach; champagne may be used, and the wine ought to be given immediately before or during a meal.

Cases of hemorrhage, shock and other forms of severe and sudden depression of the heart and central nervous system are very frequently treated by the administration of strong alcoholic preparations, such as brandy and whiskey, this treatment being based upon the belief that alcohol is a cardiac and respiratory stimulant, the grounds for which have already been examined. It is extremely difficult to estimate the value of a remedy in these conditions, and it is possible that the irritant action of alcohol in the stomach may increase the activity of the medullary centres reflexly, or that by its narcotic action it may lessen the anxiety and pain of the patient. But the beneficial effects of alcohol in these cases has been much questioned in recent years, and the belief that it is of little value is certainly more widely held at present than at any previous time; in experimental shock in animals,

Chill + fever [illegible] hot water + whiskey = dil. of skin + relief of int. congestion
In fevers lessened movement + little effect on combustion = reduction of temp., tends the [illegible]
Lessens resistance to bact., but may be outweighed by narcotic + food effects

Crile found that alcohol generally increased the danger when given in average doses, and that smaller doses had no beneficial effects, but it is quite possible that in man different results may be obtained from alcohol acting as a narcotic and removing nervous symptoms which would not arise in the lower animals.

In sudden chill with a tendency to fever, alcohol is often of great benefit, especially when taken in the form of brandy or whiskey diluted with hot water. Its efficacy here would seem due to the relief of the congestion of the internal organs by the return of the blood to the skin.

In many cases of acute inflammatory disease, the prescription of alcohol seems to be attended with benefit, while in others it seems rather to increase the severity of the symptoms. No special indications can be given for alcohol in these cases, and the physician must be guided by its effects. An old rule advised that if the pulse becomes slower, the temperature falls, the respiration is deeper, the nervous symptoms are ameliorated and the skin becomes moister after the administration of alcohol, the treatment ought to be continued; but this is merely equivalent to advising the continued administration of alcohol when it is found to improve the symptoms. The effect of alcohol in these cases is often said to be a stimulant one on the heart and central nervous system, but it would rather seem to allay the irritability of the nervous centres, and thus reduce the delirium and slow the heart and respiration by lessening the muscular movement. Moreover, the tissue waste is much increased in fever, and at the same time the food absorption is less than normally, so that many of the symptoms may be due to starvation of the tissues. The food-value of alcohol is unchanged by the presence of fever (Ott); it demands less energy from the digestive organs than fats and starchy foods, and has a higher value as a producer of energy than sugar. It cannot supply the place of the nitrogenous foods, but given along with them, may lead to a greater economy of the tissues. And Kochmann has recently shown that in starvation life may be considerably prolonged by the administration of alcohol in small quantities. Strong wines or diluted spirits are generally employed here and ought to be given in small quantities frequently. Alcohol was formerly advocated especially in septic conditions, and here it may be of value on the same grounds as in acute fevers, although it does not seem to have any specific action in septic disease, as was once believed. A protest has recently been raised against the use of alcohol in these cases, on the ground that animals subjected to alcohol succumb more readily to infection than controls which have received no treatment, and this has been shown to be true even when the dose of alcohol was proportionate to that often advised in the treatment of these cases in man (Laitinen). This is undoubtedly an objection of great weight, but it must not be forgotten that though alcohol may be deleterious in this way, this may be more than compensated for by its value as a food, and by its narcotic effects allaying the nervous irritability and prodanger of habit too great. In convalescence beers etc as food if not irrit. to stomach. N.G. in snake bite. Mild hypnotic. Large relatively doses to children & aged. & to alcoholics. Contraind in irritation – but champagne (CO_2) in vomiting of pregnancy & seasickness

moting sleep; this narcotic action may very well be conceived to be of benefit to man, while actually prejudicial to animals.

In some chronic forms of nervous disease alcohol may also be of value, although its administration must always be guarded, owing to the tendency to the formation of the alcohol habit. Thus, in some forms of melancholia and of neuralgia it gives relief, partly probably through its depressant action on the brain and partly from its local action on the digestion. Some authorities recommend the use of alcohol in small quantities in cases of distress of mind from any cause, such as grief, business anxiety or depression, and undoubtedly alcohol improves these conditions by its narcotic action on the brain. But the danger of the alcohol habit is so great that many physicians refuse to take the responsibility of prescribing the drug in these cases.

In chronic conditions of cachexia and loss of flesh in general, and during convalescence, alcoholic preparations are often advised simply as foods, and in these cases the ales, beers and porters are generally to be preferred to the others, provided always that the stomach is not irritated by them, as they contain other food-stuffs of value in addition to the alcohol.

In poisonous snake bite, alcohol is generally administered in enormous quantities, either as whiskey or brandy, but it is really of no value in these cases.

Alcohol is of value as a mild hypnotic, a comparatively small quantity taken before retiring being often sufficient to secure quiet and refreshing sleep. Beer or spirits and water is generally used for this purpose.

Brandy has a certain reputation in the treatment of the milder forms of diarrhœa, while the other spirits have no effect in this condition. The way in which it acts here is unknown.

In the prescription of alcohol, the ordinary spirits, brandy or whiskey, are very much more frequently advised than the purer preparations, as the latter are more apt to pall upon the taste of the patient. Both of these spirits ought to be diluted with at least an equal quantity of water. The wines are more used in chronic conditions, although diluted spirits may be advised here also. Beers are employed only in debility unaccompanied by gastric symptoms.

Alcohol can be given to children in relatively larger quantities than to adults, and again in old age no such reduction in the dose is required as in the case of many other drugs. Where a tolerance for alcohol has been established, the dose has often to be more than doubled in order to have any effect, and in acute febrile conditions very large quantities of alcohol are often given without intoxication, though it seems questionable whether an equally beneficial result could not be attained with much smaller doses. In gastric irritation, most preparations of alcohol are contraindicated, but champagne is often of benefit in checking vomiting, especially that of pregnancy and of seasickness, this effect being due to the carbonic acid, not to the alcohol. In nephritis and other inflammatory conditions of the genito-urinary

[illegible]
as etc. + habit. Chronic catarrh, dil. of skin vessels of face, fatty degen of liver + kid., art + art. scler. – atheroma apoplexy. [illegible] dil. of heart. chromatin disappears + cells shrink. Memory, self control etc go. Tremor. hallucinations, mania, idiocy, paralysis

tract, alcohol is generally avoided on account of its supposed effects on the epithelium.

In regard to the habitual use of alcohol by healthy persons all authorities agree that it is a luxury, that it is entirely unnecessary for the growth and maintenance of the body, but that taken in moderate quantities it is harmless, except from the danger that this may lead to the habit being formed. The habitual indulgence in alcohol to excess is more easily intelligible than some other chronic intoxications, for, unlike nicotine, alcohol is taken not only for its local effects on the organs of taste and on the mucous membranes of the mouth and stomach, but also for its action on the brain in numbing the consciousness of unhappiness, and this weakening of the higher sensibilities by drink is generally the object sought by the drunkard. He finds that under alcohol his habitual depression disappears, and he loses the sense of degradation and remorse which possesses him when sober. The depression returns in exaggerated form after the effects of the drug have passed off, but it can be removed again by the same means, and in this way the habit is formed, each successive dose being rendered necessary by the depression produced by its predecessor. This descent into chronic drunkenness is facilitated by the lessening of the self-control owing to the action of alcohol on the brain. The victim may form the best of resolutions, but his impaired will power and self-control are unable to carry them out.

The symptoms of **Chronic Alcoholism** are unfortunately common, but may be treated better in detail in connection with various forms of disease, with which they are associated more closely than with the effects produced by the medicinal use of the drug. The earliest symptoms are generally observed in the stomach, throat and larynx, and consist of a chronic catarrh, which is often accompanied by skin affections, such as injection of the cutaneous vessels (especially of those of the face), acne or pustular eruptions. The irritation spreads from the stomach to the liver and kidney, and produces fatty degeneration and necrosis of the cells. The fatty degeneration is also found in the arterial walls throughout the body, and causes atheroma and arterio-sclerosis, which may lead to small aneurysmal dilatations, ecchymoses, or apoplexy. The heart undergoes more or less fatty change, which is accompanied by dilatation and weakness. In the central nervous system, the nutrition is imperfect owing to the vascular changes, but in addition to this, alcohol has a special action on the neurons, which is betrayed by the disappearance of the chromatin granules, and eventually by shrinkage of the whole cell. The dendrites show moniliform enlargements along their course, and in the later stages the finer dendrites disappear entirely. These alterations in the central nervous system lead to impairment of memory, self-control and the other higher mental processes. Tremor, convulsive attacks, hallucinations and mania are eventually followed by idiocy and paralysis in the worst forms of the disease. The peripheral nerves seem to be acted on directly as well as through the

Acute insanity = d.t. — sudden shock or orgy brings it on. [illegible]
Beer & wine little harm. But leads to spirits. Chronic alcoholism a sign
of mental deficiency

changes in the centres, for neuritis has been frequently observed, ending in local paralysis. A form of amblyopia commencing by atrophy of the retinal ganglion cells and later extending to the fibres of the optic nerve has recently received some attention; it is much more readily elicited by methyl than by ethyl alcohol. A characteristic result of chronic alcoholism is *delirium tremens*, an acute attack of insanity, which is liable to occur after any shock, such as hemorrhage or acute disease, but which is said to be also produced by the sudden withdrawal of alcohol, and sometimes occurs without any apparent immediate cause. It is characterized by tremor, perspiration, sleeplessness, fear, excitement and hallucinations of the various senses, which differ from many other hallucinations of insanity in consisting of the multiple appearance of the same object. These objects are often animals, such as snakes, rats, dogs, but the hallucinations are not confined to those of sight, for whispering voices are complained of not infrequently.

The more severe forms of chronic alcoholism are confined almost entirely to the drinkers of undiluted spirits. Beers and wines seldom have any distinct action on the brain in themselves, unless spirits are also indulged in. The abuse of the weaker preparations of alcohol is always liable to lead to that of the stronger, however, as tolerance is established and the former lose their effect. The combination of spirits and malt liquors is said to be more liable to produce delirium tremens than the abuse of either alone.

The disastrous effects of the abuse of alcohol are seen in the statistics of the hospitals, prisons and asylums, and unfortunately these show an increase in the number of victims almost every year and in nearly all countries, but more especially in those in which the population is addicted to spirits. In Prussia in 1886–1888, 11 per cent. of the cases admitted to the insane asylums were diagnosed as directly due to alcoholic excess, while in one of the Berlin asylums the enormous percentage of 47.4 of the admissions were found to be addicted to alcohol. In France, in 1888, one eighth of the cases of suicide were due to alcoholic excess. In Paris, 72 per cent. of the convicted criminals in one year were found to be chronic alcoholists, while the proportion in Berne Canton was about 40 per cent. These numbers are officially certified to be correct, but give only an imperfect idea of the deplorable results of alcoholic abuse, as only the more extreme cases come under the categories of criminals or lunatics, and the enormous number of cases of disease directly caused or aggravated by the lesions due to alcohol escapes recognition. At the same time, it is beginning to be appreciated that chronic alcoholism itself is probably due to a mental defect, so that in a certain number of these cases of insanity and crime, the over-indulgence in alcohol must probably be considered a symptom and not a cause. Attempts have been made of late years to demonstrate that the effects of alcohol are hereditary, that the children of alcoholists supply a larger proportion of cases of insanity and crime than those of the rest of the population. The

The habit not inherited. Mental & bodily weakness is — poor resistance
Acute poisoning - Stomach tube, warmth, strych caffeine, art resp. - Ice bags to head for congestion - Chronic · withdraw gradually else dt. Opium or capsicum substituted
Ipecacuanha or apomorphine with drink. Withdraw gradually in dt. Chloral or opium

belief is widely entertained among biologists, however, that acquired characters such as alcoholism are not inherited directly, but can only affect the nutrition of the offspring. It would seem more probable, then, that the alcoholic excesses of the parent have no direct effect on the offspring, except in their nutrition at birth, but that the mental defect which leads to alcoholic excess in the one generation is inherited and leads to crime or insanity in the next. The deleterious effect of the alcoholic habit in the parent on the nutrition of the offspring is a well-established fact. It has been shown experimentally by Hodge, who states that only a small percentage of the puppies born of parents treated with alcohol survive, and further they are peculiarly liable to infectious disease, such as distemper.

The Journal [illegible] the parent [illegible] and affected [illegible]

The *treatment of acute alcoholic intoxication* is to evacuate the stomach by means of the soft elastic tube. The patient ought to be put in bed and kept warm, as there is a tendency to a marked fall in the body temperature. In case of great congestion of the brain, cold may be applied in the form of ice-bags to the head, and some authorities recommend bleeding. In cases of extremely deep unconsciousness, nervous stimulants, such as caffeine or strychnine, may be had recourse to, and, as a last resort, artificial respiration.

Chronic alcoholism is to be treated by the withdrawal of the poison, and this is best done gradually, as the immediate stoppage may lead to delirium tremens. It is often necessary to incarcerate the patient in some retreat. A large number of drugs have been advocated in these cases, some of them, such as opium, acting as substitutes for alcohol, others (capsicum) replacing the local action on the stomach. The use of opium and other narcotics may, however, lead to a craving for these which is quite as serious as the original condition. Another method of treatment, which appears to be successful in some cases, is the addition of nauseating drugs such as ipecacuanha or apomorphine to the alcohol which is supplied to the patient. The association of nausea with liquor eventually becomes so strong that alcohol in any form becomes distasteful. The organic lesions must be treated individually.

The *treatment of delirium tremens* generally consists in the use of chloral or opium to lessen the excitement. It is often necessary, or at any rate advisable, in these cases to allow small quantities of alcohol, as the sudden withdrawal may aggravate the condition.

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General anaesthesia — enough unconsciousness for operations.
Long – ether (1842) Simpson chloroform (1847)

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2. General Anæsthetics—Ether and Chloroform.

The term general anæsthetics is employed to indicate substances used to produce unconsciousness sufficiently complete to allow of surgical operations being performed. In the history of medicine there are repeatedly obscure allusions to substances used for this purpose, but it was not until the end of the first half of the nineteenth century that the era of surgical anæsthesia really opened. In 1798 Davy advised the use of nitrous oxide as an anæsthetic, but no practical use was made of his suggestion, and Wells may be said to have rediscovered this property of the gas in 1844, though his efforts to introduce it into general use met with no greater success than Davy's. Long used (U. of Pa.) ether in 1842–1843 in surgical operations, but did not give any publicity to his discovery, and the honor of demonstrating publicly the practical use of ether in surgery must be awarded to Jackson and (Why) Morton in 1846. In 1847 Simpson introduced chloroform to the medical profession as a substitute for ether, over which he supposed it to possess several advantages. Its pharmacological action had been

N_2O for short operations [illegible] induced by inhalation
Danger acc to conc. of vapor, not to amt (laws of absorption of gases)
1st effect asphyxia, [illegible] Pupils dilate. Face flushed, [illegible], [illegible] in ears etc

investigated some months earlier by Flourens, but Simpson appears to have made his investigations quite independently. Chloroform soon ousted ether in popular favor in Europe, and although in America a considerable number of surgeons continued to use it, ether had practically fallen into complete disuse throughout Europe, save in Lyons, until a few years ago. The continually increasing number of accidents in chloroform anæsthesia has, however, caused a reaction to set in in favor of ether, and it seems probable that it will once more be reinstated as the rival, and perhaps as the superior, of chloroform throughout the world. Even in 1880, however, Kappeler could write that in Germany chloroform was used exclusively.

Many attempts have been made to introduce other substances of the methane series as substitutes for the two generally recognized anæsthetics, but as yet no other has attained popular favor. Soon after the introduction of ether and chloroform, nitrous oxide gained a permanent footing as an anæsthetic for short operations.

These anæsthetics are invariably given by inhalation and not by the stomach, as it is found that the exact depth of the narcosis can be much more easily controlled by the former method. Both the absorption and excretion of these drugs occur almost entirely by the lungs, according to the ordinary physical laws of the absorption of gases by fluids. The more concentrated the vapor of chloroform in the lungs, the greater is the quantity absorbed into the blood and the deeper the narcosis. By regulating the proportion of the vapors in the air inhaled, therefore, an anæsthesia of any desired depth may be induced. The degree of narcosis and of danger is not indicated by the actual amount of the anæsthetic which has been used, but by the concentration of the vapors which have been inhaled; one patient may, in the course of a long operation, inhale and again exhale many ounces of chloroform without danger, while another may be thrown into a position of extreme peril by the inhalation of a few drops of chloroform in concentrated vapor.

Symptoms.—The action of chloroform and ether may be divided into three stages: 1, that of imperfect consciousness; 2, that of excitement; 3, that of anæsthesia.

The *first effect* of their application is a feeling of asphyxia, which is especially marked in the case of ether, and of warmth of the face and head and eventually of the whole body. The senses become less acute, the patient seeming to see only through a veil of mist, and the voices of those in the immediate neighborhood appearing to come from a distance. Ringing, hissing and roaring in the ears, and a feeling of stiffness and of inability to move the limbs herald the approach of unconsciousness. With the exception of the first feeling of suffocation, the sensations are generally pleasant. During this stage the face is generally flushed, the pupils enlarged, the pulse is somewhat accelerated, and the respiration may be rendered irregular by the sense of suffocation, or may be slightly quickened. Even at this early stage sensation is blunted.

II – Pupil still dilated. Struggling, shouting, [illegible] movements in [illegible] [illegible] [illegible] vocal [illegible] [illegible] up, flushed or cyanotic face. May be absent. Variable

III Relaxation – death face, pupils contract & ~~[illegible]~~ react to light. Reflexes go, last is closing eyelids on touching cornea. Resp. slow & shallow but regular. Pulse weak & slow. [illegible] heart slower. On recovery [illegible] [illegible] nausea after [illegible] [illegible]ssions. Body temp. [illegible] – [illegible]. [illegible] [illegible].

The *second stage* of excitement varies extremely in different individuals. In some cases, especially in children, it is entirely absent, and in others its presence may be indicated merely by ~~tremor,~~ by the stretching of the limbs, or by irregularities in the respiration, but in the majority of cases of anæsthesia it is much more marked. It often begins by movements of the arms, designed either to push away the inhalation mask or to enable the patient to rise; soon his other muscles are involved in the movement; he struggles, shouts, sings, groans, or bursts into ~~laughter.~~ The movements are not generally uncoördinated, but are evidently the result of some dream-like condition of the consciousness, and these dreams are often connected with the operation or with the surroundings of the patient before the inhalation began. They are, of course, determined largely by his natural mode of thought—one person prays aloud and sings hymns; another abuses the surgeon, the hospital and all his recent surroundings, while yet another is overcome with the fear of impending death and laments his unfortunate position. In this stage the pulse is generally quickened, the skin is flushed and often cyanotic, the respiration is extremely irregular from the struggling, and the pupil continues somewhat dilated. ~~If the anæsthetic be~~ pushed, however, the movements soon become less powerful, the muscles relax and the stage of anæsthesia sets in.

In the *third stage* the face assumes a calm, death-like appearance from the relaxation of the muscles, the pupils contract somewhat and do ~~not~~ react to light. The reflexes disappear, one of the last to go being the closure of the eyelids on touching the cornea. The pulse is generally somewhat slow and weak; the face is pale in chloroform anæsthesia, but may be suffused and cyanotic after ether. The respiration is slow and shallow, but regular. This stage of anæsthesia may be kept up for hours without much change by the repeated inhalation of small quantities, although the pulse tends to become weaker and the respiration shallower unless the greatest care be exercised, and the body temperature invariably sinks. When ~~the administration~~ ceases, the patient passes again through the excitement stage, which, however, is not generally as violent, ~~although it may be more prolonged,~~ and then often sinks into sleep, which lasts several hours. ~~Not infrequently, however, instead of sleep, nausea, giddiness~~ and vomiting continue ~~for some time after the recovery of consciousness.~~

Higher with Eth

In surgical anæsthesia, the third stage is often interrupted by short intervals of semi-consciousness and slight excitement if the administration of the drug be interrupted occasionally, as is sometimes advisable in prolonged operations.

The use of these drugs is so widespread, and the indications of danger in anæsthesia are so important that a more detailed account of the alterations observed during their use in the human subject may be inserted here.

The *pulse* is often somewhat accelerated before anæsthesia, owing to the anxiety and nervousness of the patient, and in the first, and still

[illegible] rapid in I & II - pulse [illegible] [illegible] [illegible], with progressive [illegible]. [illegible]
[illegible] & [illegible]. Resp. [illegible] I, [illegible] regular in III. Mucus may obstruct so a falling
[illegible] tongue (snoring). Dilated pupil I, II. Contracted in III; dilated with weak resp & heart & with no
pulse (or vomiting) [illegible] in IV; Rolling of eye balls. Hypersecretion of saliva & mucus.
vomiting common [illegible] after a meal. Ether = habitual intoxication as alcohol.

more the second stage, a further acceleration may occur from the same cause, although in other instances marked slowing of the pulse may set in here from reflex stimulation. When the stage of anæsthesia is reached, the pulse becomes slower and weaker than normally, and this change increases with the depth of the anæsthesia produced. It remains perfectly regular, however, in ordinary cases, and, in fact, unless the anæsthesia has reached an extremely dangerous stage. In very prolonged, deep anæsthesia the weakness of the pulse may give rise to anxiety, especially if the temperature of the body is very low.

The *respiration* is generally fairly regular until the second stage, save that the breath may be held for some time owing to the choking sensation, and a deep gasp may follow; coughing is occasionally met with, especially in the first stage of ether anæsthesia. In the second stage, the respiration is extremely irregular when the excitement is violent. The respiratory muscles are involved in the general convulsive movements, so that no air whatever can enter the lungs for several moments, and then several deep gasps may follow and load the blood with concentrated vapor. During the third stage the respiration becomes regular but shallower and slower than before the anæsthetic was applied, and if the operation be prolonged, the weakness of the respiration may give rise to alarm. Large quantities of saliva and mucus may hinder the respiration and require removal, and a common occurrence is the production of snoring from the falling back of the tongue, and this may also require attention.

The behavior of the *pupil* is of some importance in anæsthesia. During the first and second stages it is generally somewhat dilated, but as soon as complete unconsciousness is attained, it becomes rather narrower than it is normally. As the patient recovers, the slight dilatation recurs, and if the respiration and circulation be dangerously weak, this dilatation also occurs in most cases. Dilatation of the pupil in the stage of anæsthesia, therefore, indicates danger, unless it is accompanied by symptoms of returning consciousness, such as reflex movements and vomiting.

Other eye symptoms which occur in some cases are squinting and more or less rhythmic movements of the eyeball. In the beginning of the narcosis the pupil is generally directed upward and is covered by the upper lid as in ordinary sleep, but later it returns to the normal position; curious rolling movements, which are quite independent in the two eyes, often make their appearance (Kappeler, Hogyes).

The *hypersecretion* of saliva and of bronchial mucus is much more marked in ether than in chloroform anæsthesia. *Vomiting* occurs so frequently during anæsthesia that it may be looked upon rather as one of the attendant phenomena than as an accident. It may set in practically at any time, but is more often seen in the late than the early stages, and more frequently when the anæsthetic is applied soon after a meal than when the stomach is empty.

Action.—The action of ether and chloroform on the **Central Nervous System** is evidently similar to that of alcohol, although the phenomena

a) Cerebrum (sensation) backs extremities 2) genitals 3) V) b) lower brain c) cord d) medulla.
Sensory function disappears before motor.

habitually elicited in the use of the former are very rarely produced by the latter. In all three intoxications, however, there may be observed the stages of lessened consciousness, of excitement, and of total unconsciousness. Alcohol was formerly administered in very large quantities to allow of surgical procedure, and ether has not infrequently been used as a habitual intoxicant.

FIG. 6.

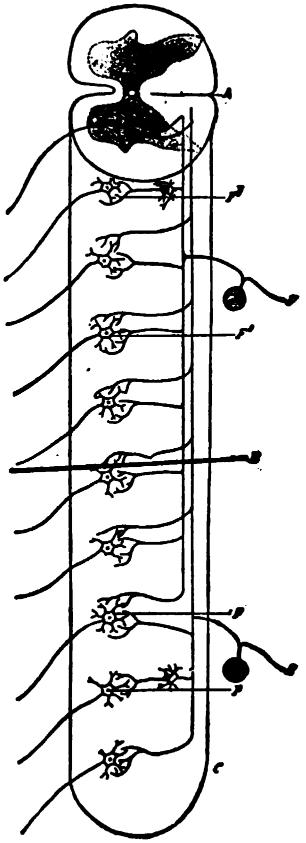


Diagram of the spinal cord. A-B part of the cord exposed to the action of chloroform, B-C part unaffected. A sensory impression traveling by the posterior root fibre D does not elicit a reflex movement, but one reaching the cord through the unaffected root E causes reflex impulses, which may be sent out by the motor cells F, F in the unaffected area, or by F′, F′ in the poisoned area. The cells of the anterior horns F, F′ and the dendrites surrounding them are, therefore, intact after the reflex arc is interrupted at some other point.

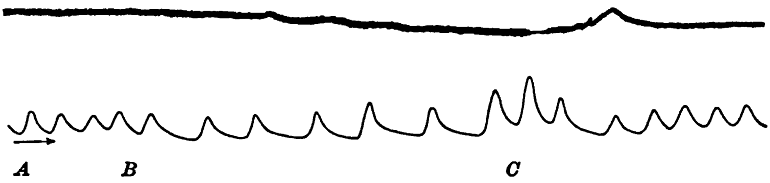
These anæsthetics produce the same progressive paralysis of the central nervous system as alcohol, commencing with the highest cerebral functions, those of self-control, and passing downwards through the lower intracranial divisions. The spinal cord is affected before the medullary centres, which are the last part of the central nervous system to become paralyzed. Some authorities believe that the motor areas of the brain are first stimulated before being paralyzed, but it is unnecessary to enter upon this question here, as it has been discussed under alcohol. The wilder excitement of chloroform and ether may be due to the greater irritation which they excite in the periphery. It may be remarked that the depression of the motor areas has been shown experimentally in the case of chloroform and ether, a much stronger electric stimulus being necessary to produce movement of a limb after these drugs than before them; their excitability by the electric current has not been tested, however, during the excitement stage. The anæsthesia is not produced equally rapidly throughout the body, the back and the extremities first becoming insensible, then the genital organs and rectum and, last of all, the parts supplied by the trigeminus. The reflexes of the spinal cord are depressed by small quantities of ether or chloroform and are finally paralyzed completely. Both of the anæsthetics affect the sensory functions before the motor. For Bernstein found in some cases that if chloroform were excluded from an area of the spinal cord by destruction of part of the pia mater, reflexes could be elicited in other parts of the cord by the

Finally medullary centres are paralyzed. Reflexes possible up to time they cease to send out impulses (stim. of sup. laryngeal = resp. response) Asphyxia may be due to failure of sensory nerves to transmit aff. impulses. i.e. [illegible] of motor. 1st reflex on V & X [illegible]

irritation of sensory nerves whose cells lay in the protected area, while irritation of nerves, the cells of which were exposed to the chloroform, had no effect (Fig. 6). In the protected area there were, of course, both motor and sensory cells, and an impulse reaching the protected sensory cell was transmitted to the neighboring and also to more distant motor cells. An impulse reaching the exposed sensory cell, on the other hand, was not transmitted to the motor cells, although these were shown by the first part of the experiment to be capable of stimulation. This experiment is best interpreted by supposing that the anæsthetics act first on the first synapse in the cord that is met by an afferent impulse. Later, however, the motor cells or their synapses are also paralyzed, as is shown by stimulation of the cord having no effect, even when the respiration is still active. Electrical stimulation of the cerebral motor areas produces movement for some time after sensation has been lost, but as the anæsthesia becomes deeper, their irritability disappears. Finally the medullary centres are also paralyzed by the anæsthetic. There is some evidence that they are first stimulated directly by chloroform and ether (page 163). The medullary centres are liable to be affected by reflex stimulation up to the moment at which they cease to send out impulses, for the respiratory centre responds to stimulation of the superior laryngeal nerve as long as the respiration continues. It is possible that the motor cells are not directly paralyzed by the drug, but can only send out impulses received from the sensory cells, and that the paralysis of these is the cause of the asphyxia.

Shortly stated, the direct action of chloroform and ether on the central nervous system is a descending depression and paralysis which affects the medullary centres last of all, and which involves the synapses on the sensory and receptive tracts sooner than those on the motor ones.

FIG. 7.



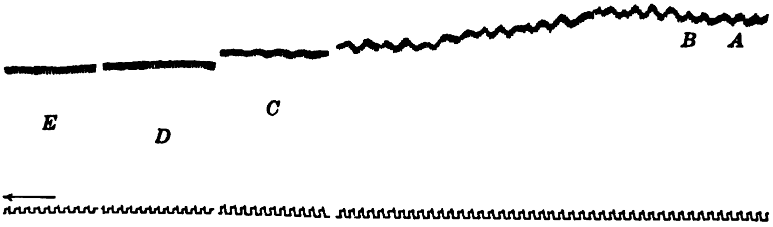
Tracings of the blood-pressure (upper) and of the respiration (lower) of a cat at the beginning of ether inhalation. *A*, normal respiration. At *B*, ether inhaled, and there follows an immediate slowing of the respiration (reflex inhibition) culminating in gasping at *C*. The respiratory tracing then resumes its normal appearance except for some slowing (central).

The action of chloroform and ether on the **Respiratory Centre** is partly direct and partly indirect. In the first stage, the respiratory movements may be slowed or stopped temporarily by a reflex action set up by the irritation of the terminations of the trigeminus in the nose and throat and of the pneumogastric in the larynx and bronchi, but this interruption is only of short duration (Fig. 7). During the [illegible] sensory [illegible] has no effect. Drug directly on center = slowing. Ultimate paralysis of center & cessation if drug pushed [illegible] effects = anaemia of medulla [illegible] Heart primary stim. of [illegible] card. inhib. center. Slow & bp. [illegible] stim. of vasomotor. It & bp. after [illegible] pulse rate & bp. [illegible] weak heart & dilated vessels.

second stage the respiration is often rendered irregular by the convulsive struggling, which produces alternately periods of asphyxia and deep gasping movements. During the third stage, the respiration is regular and no reflex disturbance occurs, because the sensibility is so dulled that the continued irritation of the nerve ends causes no reflex response. In this stage, however, the direct action of the drug on the centre makes itself manifest in the slow and shallow respiratory movements. If the drug be pushed, the weakness and slowness of the movements increase, until the respiration ceases entirely from paralysis of the centre; in addition to its direct action on the centre, chloroform depresses the respiration in deep anæsthesia by inducing anæmia of the medulla through its effects on the circulation. In man and the dog and cat the respiration is gradually extinguished, but in the rabbit the final standstill is preceded by very rapid and extensive respiratory movements.

The effects of the anæsthetics on the **Circulation** are complicated by the respiratory action, and in order to arrive at any satisfactory conclusions as to the changes in the heart and vessels, it is therefore necessary to examine their action while the aëration of the blood is carried on artificially, when the effects are seen to be partly direct and partly indirect. The first change observed in the blood-pressure tracing, after chloroform or ether is often a slowing or even a temporary standstill of the heart, due to reflex stimulation of the inhibitory centre from the irritation of the air passages; but in other cases a short rise in the blood-pressure is seen from a similar reflex action on the vasomotor centre. and this may be accompanied by extreme acceleration of the pulse arising from the general excitement. Later, however, a fall in blood-pressure is observed, and afterwards a distinct slowing of the heart. Eventually, if the administration be carried far enough, the blood-pressure falls to zero and the heart ceases to beat. The way in which this fall in the blood-pressure is produced has been the subject of prolonged discussion, but it is now generally recognized that the weakness of the heart is the chief factor and that along with this there is dilatation of the peripheral vessels. The blood-pressure in man has been found to be reduced by chloroform even in the earlier stages,

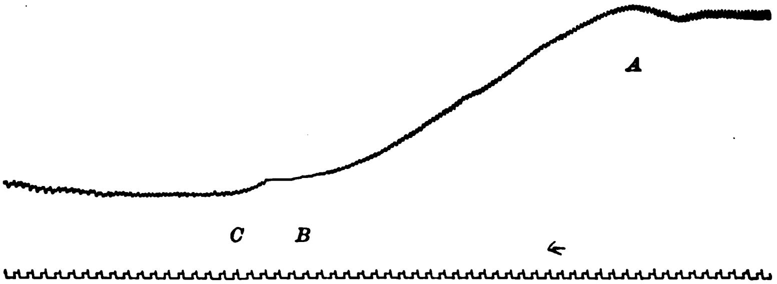
FIG. 8.



Gradual fall of the blood-pressure in a cat during anæsthesia with dilute chloroform vapor. At *A*, normal pressure. *B*, inhalation commenced and the pressure slowly falls soon afterwards. *C*, blood-pressure 5 minutes after *B*. *D*, 10 minutes after *B*. *E*, 13½ minutes later. At *E*, the respiration has ceased, but the blood-pressure is still fairly high and the pulse is satisfactory. Below the time is marked in seconds.

B.P. soon down in Chlor. ↑ usual or a little worse with Ether.
Direct weakening effect on heart (also slowing - later)

FIG. 9.



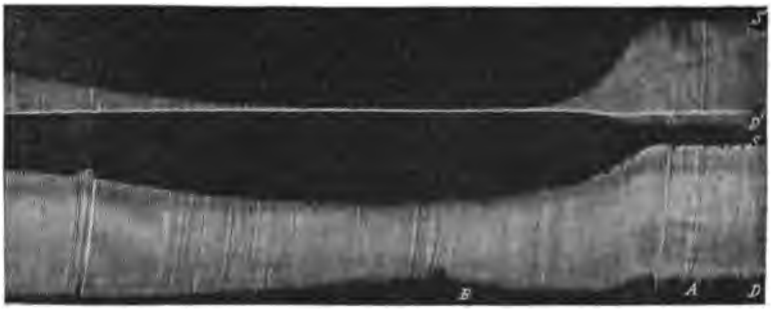
Sudden and dangerous fall in the blood-pressure from the inhalation of too concentrated vapor of chloroform during anæsthesia in a cat. At *A* the concentrated vapor began to be inspired. At *B* the blood-pressure had fallen to about one third of the height at *A*, and the pulse was so weak as to be scarcely perceptible. The chloroform mask was removed, and at *C* artificial respiration was commenced when the pulse rapidly improved in strength and the pressure began to rise.

and in deep anæsthesia the fall may be very marked. Under ether the pressure rises slightly in the first and second stages, partly from the reflexes arising from the local irritation, and partly from the muscular movements. During complete anæsthesia it falls again to slightly above the normal or a few millimetres below it, but never reaches a point indicating grave circulatory disturbance (Blauel, Cook and Briggs).

Heart.—The frog's heart under chloroform or ether beats more slowly and more weakly, and at the same time undergoes a certain amount of dilatation, all owing to the paralyzing effects of these drugs on the cardiac muscle.

The effects on the mammalian heart in deep anæsthesia are very similar. The slowing is not so marked, however, as the weakness and the dilatation, so that the rhythm of the pulse does not indicate the

FIG. 10.



Myocardiographic record of the movements of the right auricle (upper tracing) and right ventricle (lower tracing) of the dog during the inhalation of concentrated chloroform vapor. During systole the lever attached to the auricle moves from *D'* to *S'*, that attached to the ventricle from *D* to *S*. In diastole they return to *D'* and *D* respectively. At *A*, concentrated chloroform was inhaled. The excursion of the levers towards systole rapidly diminished, while that of the ventricle towards *D* was somewhat augmented. After a short time the auricle ceased in diastole, while the ventricle continued to beat, though much weakened. At *B*, the chloroform was shut off and the heart began to recover very soon afterwards.

1st weakness: auricles; ventricular relaxation. When no blood out in auricular systole, heart slows. Then standstill in diastole. .01 chlor coronary vessels - bad effect. Irrit of air passages = cardio inhibition, even stoppage; no "stop" as not directly affected

extent to which the heart is affected. The auricles are acted on by smaller quantities than the ventricles, and the former may be rendered so weak as to give practically no movement to an attached lever long before the ventricular force is very seriously impaired (Fig. 10). The first direct effect of these drugs on the heart, therefore, is a weakness in the auricular contraction and an increase in the ventricular relaxation. The diminution in the strength of the auricle progresses rapidly, while the ventricular dilatation soon reaches a maximum and is accompanied by lessened force of contraction. The auricular weakness soon becomes so great that practically no blood is expelled by its systole, and the slowing of the heart, which has not been very marked up to this point, becomes distinct. The ventricular contractions next become extremely weak and occasionally fail entirely, and soon afterwards the heart comes to a standstill in diastole. The mammalian heart suffers under extremely dilute chloroform solutions when these are perfused through the coronary vessels. Thus Sherrington and Sowton found that blood containing 0.01 per cent. of chloroform exercised a distinctly deleterious effect on the heart, and about 0.05 per cent. of chloroform was sufficient to arrest it. Loeb found that 0.4 per cent. of ether in blood perfused through the heart arrested its movements in a few minutes, so that chloroform appears to be at least eight times as poisonous to the mammalian heart as ether.[1]

This direct cardiac action of chloroform is manifested most distinctly in the third stage of anæsthesia, although it is present to a slighter degree in the earlier stages. But apart from this, the heart may be affected earlier by inhibitory activity, and this is of the gravest import in practical anæsthesia (Embley). The inhibitory centre appears to be thrown into a state of abnormal activity and the irritation of the air passages leads to reflex inhibitory impulses being sent to the heart, which responds by slowing and occasional stoppage. In the normal heart, inhibitory arrest is transient, the heart only pausing for a few seconds and then recommencing its contractions. But the heart weakened by chloroform, even in the commencement of anæsthesia, often fails to recommence beating and permanent failure of the circulation and death result (Fig. 11). This has been demonstrated experimentally in the dog (Embley) and accords with a number of observations of sudden death in man. It is liable to occur in the early stages when concentrated vapor is inhaled, while in complete anæsthesia the vagus centre appears to be less irritable. Ether injures the heart less than chloroform, and this fatal inhibitory arrest has not been shown to be induced by it.

In "weak" [illegible] heart impaired in dog.

Vessels.—It has been shown experimentally (Gaskell and Shore) that the vasomotor centre is first stimulated by chloroform, but this has very little influence on the calibre of the blood vessels or on the arterial pressure, owing to the direct action on the vessel walls. In the later stages the vasoconstrictor centre undergoes some obscure change, so that sensory impulses which normally excite it and cause

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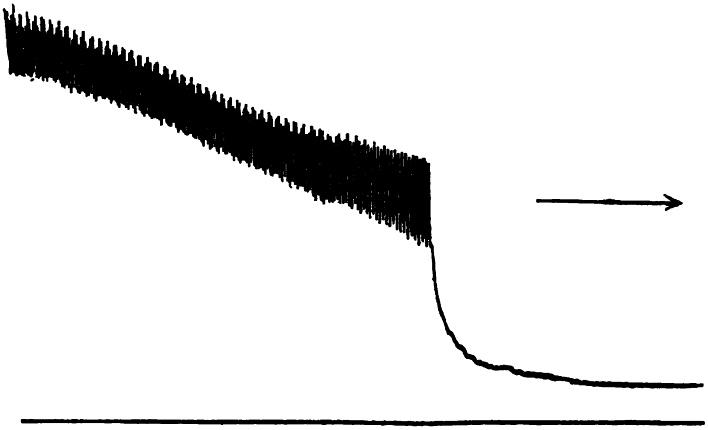
[1] In the frog's heart chloroform is said to act 30–40 times as strongly as ether.

[illegible] in vessels [illegible]
not ether [illegible] dil. centre. (of splanchnics.
[illegible] chief heart; then vessels
Const. of renal vessels after = albuminuria, anuria etc.

constriction of the vessels, now inhibit it and cause dilation of the vessels (Bayliss). The vasodilator centre continues to respond in its normal way to sensory impulses. Ether seems to have little or no direct action on the vaso-constrictor centre, but the dilatation of the skin vessels indicates that it excites the vasodilator function.

The direct action on the vessel walls seems to be of greater importance than that on the innervating centres. When chloroform circulates in the vessels in the concentrations used in anæsthesia it tends to relax them from a depressing effect on the muscle fibres; all the vessels are not equally affected, however, those of the splanchnic area dilating more readily than those of the limbs, which may even be constricted. Chloroform in higher concentration may tend to constrict also the mesenteric vessels, but this does not occur in the intact animal, in which such concentrations would prove immediately fatal to the heart.

FIG. 11.



Tracing of the blood-pressure in a dog under chloroform (5 per cent.); sudden slowing of the heart and fall in pressure from inhibitory action (Embley).

In practice, the low blood-pressure under chloroform is mainly due to the action on the heart; in less degree to the dilatation of the vessels in the abdomen.

In some experiments on the dog Kemp has noted marked constriction of the renal vessels under ether, with diminished excretion of urine and albuminuria or hæmaturia. Some writers state that albumin is found in the urine in a considerable proportion of cases of ether anæsthesia in man, which would suggest that a corresponding action is elicited here, but others have failed to detect any change except a slight diminution of the urine. The discrepancy in these results may perhaps be due to the method of administration. Ether is often given in such a way as to induce partial asphyxia and this may induce contraction of the renal vessels without a corresponding rise in the blood-pressure.

No effect directly on muscle. Ether subcutaneously often c̄ neuritis & permanent weakness. Ether & chlor dissolve reds & free haemoglobin (anemia !) Chlor chiefly carried by reds. Ether by reds & plasma.
In an. 15–30 mg chlor in 100 cc blood. Resp failure 60–70 mg/100 cc/
Ether 100–140 mgs. Resp failure 160–170 mgs. ∴ in blood anaesthesia 1/2 of that which fails
In an. contracted pupil is [illegible] as in normal sleep.

The **Muscles** and **Nerves** are not affected by chloroform or ether when inhaled, but when a frog's muscle is exposed to an atmosphere of either of them, it is weakened, loses its irritability and eventually passes into rigor mortis; the limb muscles in mammals are weakened when strong solutions (0.1–0.2%) are perfused through them, but are unaffected by concentrations which arrest the heart in a few minutes. Waller has shown that when a frog's nerve is exposed to chloroform or ether vapor in weak dilution, its irritability is at first increased; strong vapor, on the other hand, abolishes the excitability temporarily in the case of ether, generally permanently in that of chloroform, which is much the more powerful nerve poison of the two. The sensory fibres are said to be paralyzed sooner than the motor when chloroform or ether is applied to a mixed nerve (Pereles and Sachs), and some motor fibres of a trunk may remain unaffected, while others are paralyzed. The local paralyzing effects of ether have been elicited repeatedly in the human subject by its subcutanous injection, and have occasionally been followed by neuritis and permanent weakness.

Chloroform and ether dissolve the **Red Corpuscles** and free the hæmoglobin when they are shaken with defibrinated blood outside the body, and chloroform is said to retard the reduction of oxyhæmoglobin by forming a loose combination with it; Da Costa holds that ether tends to destroy the red cells during anæsthesia, and advises caution in its administration in cases in which a diminution in their numbers may be of serious import. In the blood, chloroform is carried by the red cells for the most part, comparatively small quantities being free in the plasma. It appears to form a loose combination or solution in the cholesterin and lecithin of the corpuscles. Ether is said to be more equally distributed between the corpuscles and plasma.

The amount of chloroform in the blood during the stage of anæsthesia is about 15–30 mgs. in 100 c.c. When the respiration fails the blood is found to contain 60–70 mg. per 100 c.c. (Buckmaster and Gardner). During the induction of anæsthesia the arterial blood contains more than the venous, part of the chloroform being taken up by the tissues as it passes through the capillaries. On the other hand, as the anæsthesia passes off, the venous blood contains more than the arterial, the anæsthetic taken up from the tissues in the capillaries being eliminated in the lungs. Nicloux states that in light anæsthesia from ether the blood contains about 100–110 mgs. per 100 c.c., in deep anæsthesia 130–140 mgs., while 160–170 mgs. per 100 c.c. proves fatal from failure of the respiration. The margin of safety in anæsthesia is thus narrower than is generally recognized, for the concentration in the blood necessary for anæsthesia is about half that which is fatal.

The effects of chloroform and ether on the **Pupil** present some variation in different animals, and, indeed, are not very constant in man. No entirely satisfactory explanation of their mechanism has been offered as yet. The dilatation of the pupils in the first and second stages is merely the accompaniment of the general excitement and anxiety, and is not specific. The contraction in the stage of unconsciousness is similar to that seen in natural sleep, and is evidently of central origin. The dilatation occurring during wakening or vomit-

ust before death = in paralysis of iris & pupil dilates. GI irritation with reflexes.
aliva (give atropine) Ether more irritant than chlor. Vomiting: local & central. Scanty
= urine - followed by diuresis. Chlor. esp. = fatty degen & albuminuria.
terine contractions normal in small amts. Gets to foetus - kills in gt. strength

ing is evidently caused by the same process as that of the preliminary stages. Just before death the pupil dilates, and this may perhaps be attributed to the effects of asphyxia on the muscle of the iris, and is so frequently observed in death from other causes that it cannot be regarded as a direct result of the chloroform.

The local effects of the anæsthetics on the **Alimentary Canal** and **Respiratory Passages** are confined to irritation with resultant reflexes. Thus the profuse secretion of saliva and of mucus is due to the irritation causing increased activity of the glands reflexly, and can be arrested by atropine. It has been stated that the bronchial rhonchi are due entirely to aspirated saliva, but this is incorrect, as they occur in animals to which the anæsthetic has been given through a tracheal canula. The irritation is much greater when concentrated ether fumes are inhaled than in ordinary chloroform anæsthesia.

This local irritation may explain in part the vomiting which is so often a feature of anæsthesia. The irritant vapors reach not only the throat, but also the stomach with the mucus swallowed, and irritation of either of these parts may well lead to reflex vomiting. But similar effects are occasionally induced by other methods of anæsthesia, such as by nitrous oxide, in which local irritation can play no part, so that there is probably some central effect in addition. The ordinary movements of the stomach and intestine do not seem to be influenced by anæsthesia, unless when it is accompanied by asphyxia, when the peristalsis may be increased.

The **Kidney** appears to be affected in a certain proportion of cases of anæsthesia in man, as is shown by the appearance of albumin in the urine. Chloroform induces typical fatty degeneration occasionally, while the albuminuria after ether has been ascribed to a specific vascular change by Kemp. The proportion of cases in which this organ is affected seems to vary extraordinarily, some authorities finding albuminuria in 30 per cent. of the cases where chloroform was used; while others could detect it in less than 8 per cent. Most surgeons consider chloroform far more deleterious to the kidney than ether. The secretion of urine is generally diminished during anæsthesia with chloroform or ether, from the reduced blood-pressure and imperfect aëration of the blood. After recovery from ether anæsthesia some diuresis may occur, or the urine may remain scanty for some hours.

The **Uterine Contractions** during parturition seem little influenced by moderate anæsthesia, but are somewhat slowed in the deeper stages. Chloroform and ether pass into the fœtal blood, and some experiments are recorded in which the fœtus was killed by the inhalation, while the mother recovered. This may be caused either by the direct action of the drug on the young animal, or by the low maternal blood-pressure leading to its asphyxia. It does not seem dangerous to induce a moderate degree of anæsthesia during labor in human beings, although here, too, the effects on the child are shown by an increase in the nitrogen excretion in the urine for some days.

The **Temperature** falls during anæsthesia of even short duration.

Temp. low (dil d) vessels. no movement]. Chlor. esp. disturbes nutritive processes. fatty infiltration of liver, kidney + heart, soon recovered from. In young may lead to acute yel. atrophy.

Thus Kappeler found it reduced 0.2–1.1° C. when chloroform was inhaled 15–40 minutes, and a fall of 3–5° C. has been observed during very long anæsthesia. This action is due partly to the greater output of heat through the dilated skin vessels, but mainly to a lessened heat production from the diminished muscular movement. It is not necessary to assume, therefore, as some writers do, that the anæsthetics lessen the heat production by their direct effects on the tissues in general.

Why not in sleep?

Of late years a good deal of interest has been manifested in the effects of the anæsthetics on the **Metabolism of the tissues**, and it is now generally recognized that chloroform, in addition to its action on the central nervous system, produces marked changes in the nutritive processes of protoplasm. The simpler organisms, which are devoid of nervous structure, are killed in comparatively dilute solutions, and chloroform water, therefore, prevents or retards putrefaction and the fermentation of yeasts. It seems to hinder the action of some ferments, such as pepsin and rennet ferment, when added in comparatively large quantities, but increases their activity in greater dilution. Plants cease to assimilate carbonic acid, but are not killed by chloroform except in very large quantities. In the higher animals and in man, evidences of an alteration in the processes of life and nutrition of the different organs have also been discovered, quite apart from the effects on the nervous system. Thus fatty infiltration of various organs is produced by chloroform administered repeatedly and even by a single inhalation in some cases. The organs implicated in this change are the liver, heart and kidneys more especially, but degeneration of ordinary muscle has also been observed occasionally. If this process attains a certain degree of development, it may lead to failure of the heart, but otherwise the tissues recover in the course of a few days. Traces of fatty infiltration have been observed after prolonged ether narcosis also, but they are so slight that no significance attaches to them from a practical point of view (Selbach). Given in small quantities for several months, chloroform leads to atrophic cirrhosis of the liver, and to a less extent of the kidneys, spleen and lungs, this cirrhotic change forming a sequel to preliminary fatty changes of the parenchymatous cells. In young adults chloroform has occasionally given rise to a form of liver affection which closely resembles acute yellow atrophy. In these cases after recovery from the anæsthetic, the patient becomes restless and uneasy and in a few hours delirium and coma may appear. Jaundice, cutaneous hæmorrhages, tenderness over the liver suggest an affection of this organ, and in fatal cases it is found to present the same appearance as in acute yellow atrophy, and its chemical examination proves that, as in the latter, an acute autolytic destruction of the organ has occurred (Wells).

The effects of chloroform on the nutrition of the tissues are shown in the urine secreted during and after anæsthesia, though they are more marked when it is given by the stomach from its being more

N increased. Much more unoxidized S: acetone in breath & glycosuria. So breaking up of tissues increased, but oxidation decreased. Aggravates diabetes. Often bile in urine 2 days after. Ether also lower tissues' resistance. Both in lecithin & cholesterin of blood. yes

slowly absorbed and thus acting for a longer time. The nitrogen eliminated is considerably increased, and the sulphur shows a similar augmentation, and these would seem to indicate an increased destruction of nitrogenous bodies in the tissues. In the normal urine, the sulphur appears partly in the form of sulphates, partly in forms in which it has undergone less complete oxidation. After chloroform the proportion of these constituents is changed, the unoxidized sulphur forming a much larger part of the total than normally, and apparently occurring in a substance nearly allied to cystin (Kast and Mester). This indicates that while the breaking up of the nitrogenous tissues is greater than normal, the oxidation is not so perfect, and another fact pointing in the same direction is the not infrequent occurrence of acetone in the urine and breath and of glycosuria (Becker). It has long been recognized that diabetes is liable to be aggravated by chloroform anæsthesia, and some fatalities after chloroform seem due to this action. The sugar of the blood has been found to be increased, and the glycogen of the liver is diminished or entirely absent after chloroform; this is, according to Paton, the effect of a specific action on the liver cells, which form glycogen into sugar much more rapidly than usual; ether has a very much less powerful action on them. Bile pigment is said to occur in the urine in a considerable number of cases of anæsthesia with chloroform, especially one or two days after the administration. The chlorides and acidity of the urine are augmented and this has sometimes been regarded as evidence that chloroform is decomposed in the tissues, but the chlorides are also increased by ether though not in the same degree.

These effects of chloroform on the metabolism resemble very closely those of phosphorus poisoning, and have, like them, been ascribed to autolysis and the formation of acid in excess in the tissues. They seem to occur only after those substances of the fatty series in which chlorine is substituted, ether having little or no effect in producing fatty degeneration or in changing the proportion of the sulphur compounds in the urine.

Immunity.—Anæsthesia with chloroform or ether reduces the resistance of the tissues and renders animals more susceptible to the invasion of bacteria and to the action of toxins.

Distribution in the Body.—When chloroform or ether is absorbed from the lungs, it is carried all over the body by the blood, but is not equally distributed throughout the tissues. It has been mentioned already that a loose combination exists between chloroform and the lecithin and cholesterin of the red cells, and it was to be anticipated that those organs which are richer in these constituents would contain larger quantities of the drug. As a matter of fact, both chloroform and ether are found in larger quantities in the brain than in the blood, liver or muscles, which is in conformity with the theory of Meyer and Overton regarding the causation of narcosis (page 127).

The **Excretion** of both ether and chloroform takes place mainly by the lungs. Whenever the partial pressure of the vapor in the alveoli

Partial pressure in alveoli less than in blood, is excreted. Elim. at once to 24 hrs.
lungs, urine, sweat, milk. Chlor 3½ x as depressant on cns as ether (Richards)
So ether given in greater conc. – hence salivation, sensation of asphyxia, coughing.
% for narcosis & damage to heart & resp closer with chlor than ether

falls sufficiently far below that in the blood to loosen the combination between the anæsthetics and the constituents of the blood, the drug diffuses back into the alveoli, and thence passes into the air. Most of the anæsthetic is eliminated very rapidly, but traces of chloroform are said to be found in the breath for 24 hours after the inhalation and even longer in cases in which there is a tenacious mucous secretion from the bronchi. As far as is known this is the only way in which ether is excreted, but small quantities of chloroform escape by other channels, for it has been found in the urine, and is said to occur in the perspiration and the milk.[1]

Differences Between Chloroform and Ether.—Ether and chloroform resemble each other closely in their general effects, but differ in certain points of importance. Thus ether has a much weaker narcotic action than chloroform, for Spenzer found that 1.5–2.5 volumes per cent. of ether vapor in air produced only incomplete anæsthesia, that 3–3.5 per cent. induced narcosis in 25, and 4.5 per cent. in 15 minutes, while 6 per cent. stopped the respiration within ten minutes; Rosenfeld obtained no narcosis with 0.5–0.7 volume per cent. of chloroform, complete narcosis with 1 per cent. only after 30–45 minutes, and respiratory standstill with 1.5 per cent. in the course of ¾–2 hours after the inhalation commenced.[2] So that chloroform is about 3–3½ times as depressant to the central nervous system as ether, while, on the other hand, its action on the heart is at least 8 times as great as that of ether. Ether has to be given in more concentrated form to produce anæsthesia, and, therefore, produces more irritation of the air passages, as shown by the greater secretion of saliva and mucus, by coughing, and by the sensation of asphyxia. Dreser has shown, however, that if air containing less than 6 per cent. of ether be inhaled, this irritation and feeling of suffocation is not very marked. Anæsthesia is produced with greater difficulty, more slowly and often less perfectly than with chloroform, and the stage of excitement is generally more violent and prolonged. But the pulse is not nearly so much affected as by chloroform; it may be somewhat slower than usual, but is full and strong. The concentration of chloroform which is necessary to produce anæsthesia is very close to the concentration which causes serious impairment of the heart's action, while, on the other hand, 3½ per cent. ether vapor is sufficient to cause narcosis, but a very much stronger concentration is required to cause a dangerous condition of the heart. In the same way the difference in the concentration required to produce anæsthesia and that which will stop the respiration is very much smaller in chloroform than in ether, and the anæsthetist has thus more leeway when he uses the latter. The changes in the metabolism following the use of chloroform are not produced to the same extent, if at all, by ether.

Regarding the **Choice of an Anæsthetic**, it must be said that each has h margin of safety for ether greater than chlor. Chlor less exciting, quicker less muscular activity, greater relaxation, less rapid evaporation in hot weather, open lights, cautery. Chlor contraindicated in [illegible] fatty degen. of heart & renal disease. May get it with chlor & continue with ether. False teeth, tobacco, mucous, tongue may block [illegible] asphyxia.

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[1] The statement that some carbon monoxide is formed in the tissues from the oxidation of chloroform appears to be erroneous.

[2] Other investigators have found different absolute values from these, but the relative strength of ether and chloroform is generally held to be about 1 to 3. (Honigmann.)

Direct action too. Chlor fatalities 1 in 3000 Ether 1 in 10 to 15000

its advantages, but that ether is less liable to cause dangerous symptoms than chloroform, and ought, therefore, to be used wherever special circumstances do not indicate the latter. Chloroform is always preferred by the patient, for it causes less irritation and less feeling of suffocation, and it is often preferred by the surgeon because it induces anæsthesia sooner and less of it is required. In cases where excitement is to be avoided as much as possible, or in which a very deep anæsthesia with complete muscular relaxation is required, and in irritable conditions of the air passages, chloroform ought to be used rather than ether. In the case of drunkards, ether sometimes fails to induce deep anæsthesia, and in very hot climates anæsthesia with ether may be difficult and unpleasant to induce owing to its rapid evaporation, so that in these cases chloroform may be necessary. Lastly, where artificial lights are necessary (except the electric incandescent), or where the actual cautery is to be used, ether is dangerous on account of its inflammability, and chloroform is indicated. On the other hand, chloroform is specially contraindicated in cases of fatty change of the heart and in renal disease. The disadvantages of both anæsthetics may often be avoided by inducing unconsciousness by chloroform and prolonging it by small quantities of ether. The effects of the prolonged use of chloroform are avoided in this way, and at the same time the excitement is less marked, and less irritation of the air passages is elicited than if the anæsthesia had been induced by concentrated ether vapor.

The **Dangers of Anæsthesia** are caused only in part by the direct action of the ether or chloroform, for fatal accidents have occurred from objects such as false teeth or tobacco plugs falling into the air passages and causing asphyxia, while vomited matter has been drawn into the larynx in some cases. Very often the relaxation of its muscles permits the tongue to fall back into the throat, rendering the breathing labored and stertorous; this is at once relieved when the tongue is drawn forward. The accumulation of saliva and mucus or blood in the throat may lead to similar symptoms. In these accidents the chloroform or ether is only indirectly the cause, but in a large and ever-increasing number of cases, the fatal effects must be ascribed to the direct action of the anæsthetics. The proportion of accidents during anæsthesia is very difficult to estimate, and great discrepancies occur in the statistics of different surgeons. Thus, in one of the London hospitals, one death occurred from chloroform in 1,236 cases of anæsthesia; Juillard gives one in 3,258, McGuire one in 15,000, as the proportion of fatalities, while Lawrie gives a series of over 40,000 cases without a single death. A fair average would seem to be one death in 3,000 chloroform inhalations. The statistics of ether fatalities also vary from one death in 3,000 to one in 16,000 cases, but probably one in 10,000–12,000 cases would represent the average mortality.[1]

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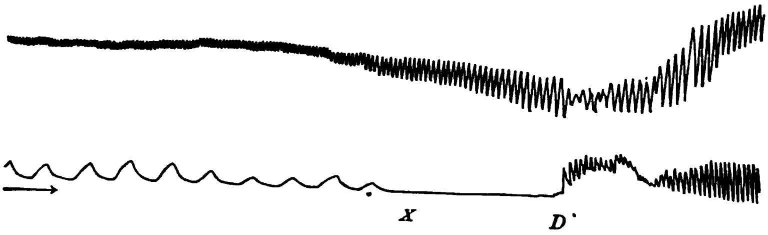
[1] Gurlt's careful statistics of 330,000 cases of anæsthesia gave a mortality of 1 in 2,000 for chloroform and 1 in 5,000 for ether, but these both seem unusually high.

Death in chlor (less ether) due to 1) direct action on a weak heart + vessels 2) struggling 3) reflex inhibition.

A very prolonged discussion as to the **Cause of Death** in these cases has been carried on, and even now there cannot be said to be any unanimity of opinion on the subject. A fatality may occur practically at any stage of the anæsthesia, and the accounts of its onset and symptoms differ exceedingly. In the majority of cases it is stated that the pulse suddenly disappeared, and the breathing either ceased at the same moment or after one or two weak inspirations. In others the respiration is stated to have ceased before the pulse, and in several the heart-beat could be felt or heard after the pulse ceased. A very considerable proportion of the fatalities under chloroform occur early in the anæsthesia, often before the operation has been begun, and these have generally been regarded by anæsthetists as due to a reflex arrest of the heart. This has been disputed by experimental investigators, ~~and, as in~~ these accidents it is impossible to make exact observations, owing to the necessity for prompt measures for resuscitation, it has often been denied that fatalities occur from this cause. The subject has recently been the subject of prolonged research by Embley, who has triumphantly vindicated the position of the practical anæsthetists by showing that fatal arrest of the heart may occur in early chloroform anæsthesia through excessive inhibition of the weakened heart (page 163). This danger does not seem to be caused by ether to the same extent, and this is in accordance with its much weaker effects on the heart. These early fatalities in chloroform anæsthesia are due in part to the chloroform already absorbed, in part to reflexes arising from its irritant action and from the excitement and struggling.

FIG. 12.



Tracings of the blood-pressure (upper) and of the respiration (lower) of the cat in the last stage of ether anæsthesia, failure of the respiration. At *X* the ether was shut off, and at *D* artificial respiration was begun. The oscillations on the respiratory tracings after *D* are due to the artificial respiration. The heart continues to beat after the failure of the respiration. The pulsations increase in size, not from an increase in the strength of the heart, but from the slowness of the beat, which gives time for the arteries to empty themselves between each pulse.

But fatal accidents may occur in anæsthesia from chloroform or ether, by the action on the organs after the danger of reflexes has disappeared, from the depression of the central nervous system. The explanation of these fatalities has been much disputed, the view having prevailed formerly that while ether paralyzed the respiration without affecting the heart, chloroform acted first on the heart and paralyzed it before the respiratory centre. In 1889 some criticisms by the *Lancet* of the results of experiments in Hyderabad led the Nizam (Prince) of that province to appoint a commission, including Sir

In both eth. + chlor resp stops before circ (which is greatly weakened) Hence artificial resp may = recovery. Resuscitation of heart depends on conc. of vapor (if strong substance damaged. If weaker only reflex. inhibition)

Lauder Brunton, to investigate the question, and after experimenting on over 600 animals, this commission came to the conclusion that death during chloroform inhalation is always due to arrest of the respiration. This decision has been subjected to much criticism, and there is no question that the alterations in the circulation produced by chloroform were not properly appreciated, or, at any rate, were not sufficiently emphasized in the report. The condition when the breathing fails during deep anæsthesia varies with the concentration of the vapor. If very dilute chloroform or ether be inhaled, the respiration always ceases several minutes before the heart, which continues to beat fairly strongly at first but rapidly becomes weaker. If more concentrated vapor be used, the respiration again ceases before the heart, which is, however, much weakened and comes to a standstill after a short interval; and as the concentration is increased, the weakness of the heart, at the moment when the respiration fails, also increases, and the interval between the arrest of the respiration and of the heart-beat becomes shorter. Finally, when air saturated with vapor is inhaled, the interval between the two is so short as to be inappreciable (Fig. 13). When concentrated vapor of either chloroform or ether is inhaled, the pulse may be so weak as to be no longer perceptible before the respiration ceases, and the anæsthetist, therefore, believes that heart failure has been the cause of death, but if the movements of the heart be registered directly, it is found beating as long as the respiratory movements are carried on. The importance of the condition of the heart is further shown by the results of attempts to resuscitate the animal after the respiration has ceased; for if artificial respiration be commenced at once, the animal can invariably be restored to life, provided the heart has not been weakened too much; but if concentrated vapors have been inhaled, the

FIG. 13.

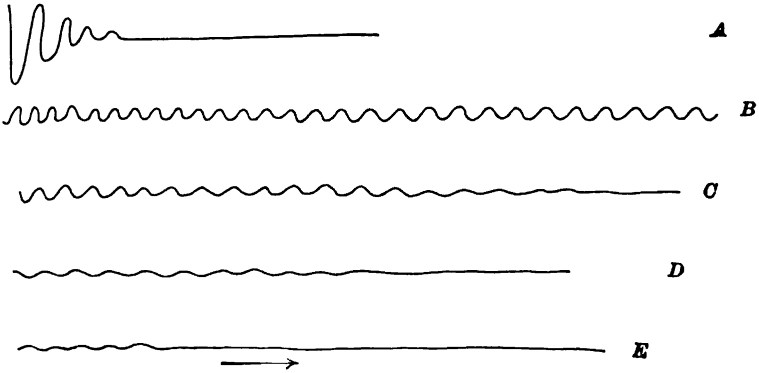


Diagram representing the state of the heart at the failure of respiration from an anæsthetic (chloroform or ether). *A* represents the respiratory movements, which cease very early in the tracing, *B* the pulsations of the heart at this point if the anæsthetic vapor has been much diluted with air, *C* if it is of medium strength, *D* if very concentrated, and *E* if saturated. The heart pulsations are recorded by the mercury manometer.

Low b.p. may cause anaemia of centers & failure of resp. Blood after death dark from asphyxia. ~~Heart dilated.~~ Degenerations. Apparatus useless as don't allow for individual variations. Take too long (1/2 hr) if a safe one used. Ordinarily a cone ~~that~~ would be fatal if long [illegible] used. until reflexes disappear.

heart is unable to carry on the circulation, and the animal cannot be resuscitated.

Hill has recently pointed out that the failure of the respiration may be caused in part by the anæmia of the central nervous system from the fall in blood-pressure. The weakness of the heart induced by chloroform is therefore fraught with double danger, for not only is the circulation imperilled by it but the respiration is indirectly weakened.

From a practical point of view, it is of comparatively little importance whether there are a few fluttering beats of the heart after the last inspiration or not. The all-important question is whether the heart has been so injured as to be unable to carry on the circulation, and this is decided by the concentration of the vapor that has been inhaled. It has been mentioned already that ether acts very much less on the heart than chloroform, and this is really the reason why ether is so much the safer anæsthetic. Even when dilute vapor of chloroform is inhaled, the heart is considerably injured when the respiration ceases, while unless very concentrated ether fumes be inhaled, the weakness of the heart is very much less. In the inhibitory cardiac arrest also, the concentration in which the chloroform has been inhaled is the all-important factor, for if the heart has been seriously damaged the arrest is final, while when less concentrated vapor has been used the heart overcomes the inhibition and resumes its contractions.

The autopsy in cases of death by chloroform or ether shows no specific lesions. The blood is often dark colored from the asphyxia, and the heart is found dilated. Irritation of the respiratory passages may be present in ether poisoning, and the odor of the anæsthetic may be recognized in the different organs. Microscopic examination may show some alterations in the cells of the respiratory centre and cardiac ganglia, fragmentation of the heart muscle, and some degeneration of the liver, kidneys, spleen and heart after chloroform (Poroschin).

Apparatus and Principles.—The principles on which the safe production of anæsthesia is based, then, are comparatively simple, but their interpretation into practice has given rise to various methods. A large number of inhalers have been introduced with the object of permitting of only a certain degree of concentration of the vapors. But the great majority of these are entirely erroneous in principle, the concentration of the vapor being determined by the character of the respiration of the patient, and the number of accidents has not been appreciably reduced by their use. In one of these the amount of oxygen available for respiration was found to be reduced to 5 per cent., while the carbonic acid had risen to 7.8 per cent. after two minutes' respiration. This mixture of gases is insufficient to support the combustion of a candle, and is very near that which is immediately fatal to animal life. In another the concentration of the vapor was found to vary between 1.2 and 16.4 volumes per cent. Several apparatus have recently been constructed on correct principles, which allow of an exact gradation in the strength of the vapor inhaled, but

Shallow resp (in giving anaesthesia) necessitates more conc. deep than gasping when exchange of gas air in alveoli direct - less by diffusion. Watch breathing + reflexes. Pulse normally irregular in II. Resp better + sooner guide in III.

they are exceedingly cumbrous, and while they might be used in hospitals, are certainly not available for ordinary practice. The advantage of this principle of measuring the concentration of the vapors is further only relative, for it has been shown that vapors so dilute as to be absolutely safe do not induce anæsthesia within a reasonable time. Thus 1 per cent. chloroform seems to be practically safe, but no surgeon will wait ½–¾ hr. for the anæsthetist. To induce anæsthesia, therefore, vapors have to be used which would in time be fatal, and only after the reflexes disappear is it possible to reduce the concentration to the point of absolute safety. The responsibility of the anæsthetist is, therefore, lessened, but by no means entirely removed by these methods. In the vast majority of cases, however, much simpler apparatus is used, and the ordinary mask or towel on which the anæsthetic is poured is not responsible for a larger proportion of accidents than the more complicated forms of apparatus. When no inhaler is used, the anæsthetist attempts to regulate the concentration of the vapor according to the symptoms, and this can be done with complete success by watching the respiration closely. If the breathing be shallow, much less concentrated vapor is inhaled into the alveoli than if it be deep and gasping, for in ordinary respiration the air in the smaller bronchioles and alveoli is not exchanged directly with every respiration, but only by a process of diffusion from the larger air passages. The deeper the respiration, however, the further does the vapor penetrate and the lower the concentration needed to change the quantity in the blood. An experienced anæsthetist, by watching the respiration, removing the mask during deep breathing and replacing it when it becomes steady, can regulate with sufficient nicety the concentration of the anæsthetic in the alveoli and thereby the quantity in the blood. When anæsthesia has been attained, he of course ceases the administration until the return of the reflexes indicates awakening consciousness, and even then applies much smaller quantities than were necessary at first. This method of inducing anæsthesia requires the anæsthetist to watch only the respiration and the reflexes, and is that advised by Simpson and his followers (see Hyderabad Commission Report). A further safeguard has been sought for in the condition of the pulse, and this would seem the natural consequence of what has been stated above as to the importance of the condition of the heart. The pulse, however, is not very reliable as a guide in anæsthesia, for in the second stage, in which a certain number of fatalities occur, it is quickened by the excitement and may be irregular, and only gives indications of danger when it is too late to take measures to prevent it. In the third stage it may become gradually weaker, and thus indicate approaching danger, but if the respiration be watched the warning is given earlier. A large number of anæsthetists advise, however, that pulse and respiration both be watched, and this would seem to be the safest method, provided always that the anæsthetist does not depend on the pulse too much for indications of danger, and does not allow it to distract his attention from the more important indications given by the respiration.

Anxiety before anaesthetic possibly give morphine or chloral. Not contra in valvular disease unless marked insufficiency or dropsy. In fatty degen — chlor bad. Ether in it may cause bad strain. Chlor in bronchitis + catarrh (less irrit.) Not in Bright's, or in repeated administration; neither in brain tumor or anaemia.

Stomach empty. hot water bottles, blankets, loose clothing. Remove false teeth, [illegible] freely [illegible] via head

Preliminary Examination.—Before anæsthesia, a careful examination should be made of the condition of the patient, and if there is great anxiety and excitement, a hypodermic injection of morphine may be given beforehand, or chloral may be prescribed, but these are rarely necessary. Valvular diease of the heart does not contraindicate an anæsthetic unless there are marked symptoms of inefficiency, such as dropsy or œdema. In fatty disease of the heart, on the other hand, chloroform is to be avoided, and if it seems extensive, ether is also dangerous from the strain put on the circulation during the excitement. Chloroform is liable to induce fatty degeneration of the heart, and for this reason it would not seem advisable to use it in successive operations on the same patient. Atheromatous arteries are dangerous from the tendency to apoplexy during the second stage also, and if anæsthesia is absolutely necessary, an opiate ought to be given previously. Anæsthesia is said to be dangerous in cases of brain tumor, and this may possibly arise from the fragility of the vessels. In cases of bronchitis and catarrh of the air passages, chloroform is to be preferred to ether as it is less irritating, while in Bright's disease chloroform is generally more injurious than ether from the resultant albuminuria and tendency to fatty degeneration, although ether is also believed by many to disturb the renal functions. Advanced diabetes contraindicates anæsthesia, the sugar increasing in the urine afterwards and coma and death sometimes supervening in the course of a few days. Da Costa recommends that where there are symptoms of anæmia, an examination of the blood should be made before anæsthesia, and states that where the hæmoglobin is found to be deficient, great care is necessary and that where it is lower than 50 per cent. of the normal, an anæsthetic is contraindicated.

Practical Anæsthesia.—The patient should have a light, easily digested meal 2–4 hours before, so that the stomach may be empty and vomiting avoided as far as possible. The bowels should also be regulated the day before for the same reason. He should then be laid on a table of suitable height with a low pillow, and should remove false teeth and any other foreign object from the mouth. The clothing about the neck, chest and abdomen is to be loosened or removed to allow of perfectly free respiration, but warm blankets or warm bottles should be applied as far as possible to prevent the fall of temperature if the operation is likely to be a long one. The eyes are closed in order to protect the conjunctiva from the irritating vapor. The anæsthetic is then applied on a towel or on a mask, which ought to be freely permeable by the air, and ought not to fit closely to the face. It must be remembered that the air passes through cloth with much greater difficulty when it is wet by the saliva and mucus, and that a mask which is freely permeable at the commencement of an operation, may lead to asphyxia after it has been soaked during the first and second stages. The patient is instructed to breathe as regularly as possible, or to count from one upwards, and some of the anæsthetic is dropped on the mask. If the breath be held, the mask should be

When gasping remove mask ~~[illegible]~~ then replace ~~[illegible]~~ or pain returns put on
reflex stoppage of resp. then a gasp. If too conc. = resp. failure from direct action on centre
lower head to help heart weak because of resp. stoppage. Artificial resp. Press over heart
Drugs of little good as absorption too poor. Better intravenous or intracardiac of saline
Adrenalin

raised a little from the face, as the next inspiration will be a very deep one. During the excitement stage the respiration is irregular, and great care must be taken to avoid the inhalation of too concentrated vapor. As soon as the conjunctival reflex disappears, the mask is removed, and is replaced only when it reappears or when the patient evinces signs of pain. Throughout the anæsthesia care must be taken to prevent any interference with the respiration by the operator leaning on the thorax or abdomen. Very often stertorous respiration sets in from the tongue falling back into the throat, and this has to be remedied by pressing forward the angle of the jaw, or if this is not sufficient, by pulling out the tongue with a blunt-pointed forceps. Vomiting is a very common occurrence in anæsthesia, and when it sets in the head is turned to one side and the vomited matter removed with a sponge.

A more serious accident is the failure of the respiration. A reflex arrest often occurs in the first stage, but is not of importance in itself, but only from the deep gasping inspiration which follows it. If the anæsthetic be given too long in concentrated form, however, the respiration fails from direct action on the centre, and this demands immediate attention. The head ought to be lowered at once, and the lower limbs elevated, in order to drive the blood to the head as far as possible and thus remedy the anæmia of the brain from the weakness of the heart that accompanies the cessation of the respiration. The epiglottis must be raised by pressing forward the angles of the jaw (Hare), or by dragging forward the base of the tongue with hook or finger. Artificial respiration in one or other form ought to be commenced at once, and carried on as long as is necessary; a large number of methods of performing artificial respiration have been proposed, but they can only be taught in a practical class and need not be entered upon here.[1] If the pulse is weak, intermittent pressure over the heart may aid it in carrying on the circulation, and it has been proposed to pass one hand up under the ribs, and then press the heart between the two hands and aid it in expelling its contents. If the heart stops at this stage, there is little hope of reviving the patient, although this can often be done in animals by kneading the heart between the two hands. Various drugs have been recommended in these cases, but it is exceedingly questionable whether they are really of service; alcohol, ammonia and ether have been injected subcutaneously, and may conceivably cause such local irritation as to reinstate the respiration reflexly, although this is improbable. Strychnine, caffeine and atropine have been injected as respiratory stimulants, and digitalis to strengthen the heart contraction; as a matter of fact, however, if the circulation is strong enough to cause the absorption of these drugs and carry them to the respiratory centre and the heart, the patient will recover with the artificial respiration alone, while on the other hand, they are of no value unless absorbed. Nitrite of amyl is often given by inhalation

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[1] For a comparison of the efficacy of different forms see *Schäfer*, Medico-Chirurgical Transactions, vol. lxxxvi., supplement, 1904.

Reflex stoppage (1) heart very dangerous. [illegible]. Atropine into heart by hyp
Very little of [illegible] after an. reached in long operations. After operation - keep warm
For prolonged vomiting - suck ice, vinegar vapor, or bismuth, lavage. Keep flat, as
do otherwise would = cerebral anemia. Don't commence op. until wholly
"under" as reflex inhib. (1) heart 2) shock

in cases of accident, but the blood-pressure is so low already that there really seems no advantage in reducing it further, and amyl nitrite can have no other action. In animal experiments, the best results are obtained by the intravenous or intracardiac injection of adrenalins in saline solution.

Sudden arrest of the heart is the most dangerous accident of anæsthesia, and, as Embley has shown, is due to inhibitory stimulation acting on the weakened heart. The treatment consists in inversion, artificial respiration, and massage of the heart. Atropine should be injected in order to paralyze the inhibitory mechanism, and in view of the arrest of the circulation it might be thrown into the heart directly by means of a long hypodermic needle.

In the course of very long operations it is recommended to allow the patient to almost recover consciousness at intervals, but this is often impossible without interfering with the course of the operation. It must be remembered that in prolonged anæsthesia comparatively small quantities are required to maintain unconsciousness when it is once completely reached, and at the same time that, owing to the fall of temperature and the prolonged action of the drug, the quantity necessary to produce cessation of the respiration and the heart is much smaller than during shorter operations. In order to induce anæsthesia within a reasonable time, comparatively strong vapor may be used, but as soon as unconsciousness is reached, the vapor ought to be diluted as far as is compatible with the continuation of the narcosis.[1]

On the completion of the operation, the patient seldom requires further attention from the anæsthetist; after prolonged anæsthesia heat may be applied by warm bottles, etc., as the temperature often continues to fall for some time after the administration of the drug has ceased. If vomiting persists after the recovery of consciousness, ice may be sucked, or bismuth may be prescribed. The inhalation of vinegar has been recommended and relief is sometimes given by lavage of the stomach.

The patient should always be placed in the recumbent position when possible, as otherwise the weakened heart tends to drive the blood in the direction of least resistance, that is, downwards, and in the depressed condition of the vasomotor centre, this is not counteracted by the contraction of the arterioles of the abdomen, and anæmia of the brain and syncope are liable to result. The operation ought not to be commenced until anæsthesia is complete; otherwise reflex inhibition of the heart or shock may result and lead to fatal results.

Various drugs have been advised as preliminaries to anæsthesia, generally with the object of preventing the reflex arrest of the respiration and heart. Thus atropine and sparteine have been proposed to paralyze the vagus, and to arrest the mucous secretion and vomiting,

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[1] In anæsthesia with measured percentages of chloroform, Alcock found it best to commence with vapor of one per cent., rising to 2 per cent. after two minutes and to 2½–3 per cent. in five minutes; this strength was continued until anæsthesia was attained after which the concentration was reduced to 2 per cent. and further to 1 per cent. in the course of 20 minutes.

To obviate unpleasant irrit & reflex effects - morphine .01-.025, N_2O, ethyl chloride. Late dangers Chl: heart liver & kidney changes diabetic coma; ether:- bronchitis, pulm. oedema, pneumonia.

and spraying of the nose with cocaine has recently been advised to paralyze the sensory terminations and so prevent the irritation which sets up the reflexes. It has been proposed to dilute ether or chloroform vapor with oxygen instead of air, but there seems no theoretical reason why this should have any advantages, and in practice it has been used in too limited a number of cases to allow of trustworthy inferences. In order to avoid the unpleasant suffocating effects of ether and to permit of less concentrated vapor being used, the injection of 0.01–0.02 G. (⅙–⅓ gr.) of morphine has been advocated as a preliminary to ether anæsthesia, and this has become a routine procedure in some clinics from which satisfactory results are recorded. In others some less unpleasant anæsthetic, such as nitrous oxide or ethyl chloride, is used to induce anæsthesia, which is afterwards maintained by ether.

Of late years a good deal of interest has been excited by the discovery that the perils of anæsthesia are not over when consciousness returns, but that fatal consequences may follow several days later. These late fatalities are due to fatty changes of the heart, liver and kidneys or to diabetic coma in the case of chloroform, to bronchitis, pulmonary œdema and pneumonia after ether. No reliable data are as yet available as to the frequency of these sequelæ, as it is very difficult to distinguish between the results of the anæsthetic and the ordinary forms of disease. Even the proportion of cases in which albuminuria occurs after chloroform seems to vary remarkably in different hospitals, for it is given as low as 5 per cent. by some authors and as high as 30 per cent. by others; this may perhaps be explained by differences in the duration of the anæsthesia. The irritant effects of ether and the liability to pulmonary affections afterwards have been so evident that some surgeons have returned to the use of chloroform, believing that the late effects in ether claimed as high a proportion of victims as the more immediate effects of chloroform. This irritant action of ether may be avoided to some extent by allowing the vapor to be inhaled in a more dilute form than is often used in inducing anæsthesia. And there is reason to believe that the pulmonary effects are often intensified by the air inhaled being chilled by the evaporation of the ether, and that they may be lessened if this is avoided by suitable inhalers.

Various **Mixtures of the Anæsthetics** have been advised at different times. Of these the ACE mixture (alcohol 1, ether 2 and chloroform 3 parts by volume) is the best known. Its use has, however, been attended with numerous fatalities, as was only to be expected from a consideration of the volatility of the different ingredients. Ether, being the most volatile, is first inhaled, and then chloroform, and last of all the alcohol. The safe concentration of ether is, however, much greater than that of chloroform, and a vapor which may be perfectly safe as long as it consists of ether for the most part, may become exceedingly dangerous when it consists of chloroform. This method, therefore, increases the responsibility of the chloroformist by leaving him in complete ignorance as to the composition of the anæsthetic at any given time. The same criticism applies to a mixture of

[illegible] very dangerous as diff. conc. (less needed. however)
Ethyl Chloride C_2H_5Cl = short. no after effects. In sealed tubes – very vol. Anaesthesia in 2–5 min – not complete relaxation. No excitement, not unpleasant, pulse slow, resp. deep
Fatalities 1 in 3000. little harmful effect on circ.
Pental dangerous

Ethyl Bromide – quick – little depression – must be colorless – [illegible]

anæsthetics advocated by Schleich and containing ether, chloroform and petrol, which enjoyed a brief popularity some years ago.

The chief argument in favor of mixed anæsthetics is that together they are more powerful than twice the quantity of either alone. This has been shown to be the case by Honigmann and is due to the fact that they render each other less soluble in water and are therefore more readily absorbed by lipoids (Fuehner). But the practical difficulties in the administration of definite quantities have not as yet been solved.

Ethyl Chloride (C_2H_5Cl) has been advocated of recent years as an anæsthetic for minor operations and examinations, and possesses the advantages of acting very quickly and of leaving no after effects except occasionally some nausea, the patient generally feeling perfectly well in a few minutes. It is kept in sealed tubes and inhaled through a mask as it is extremely volatile, boiling at about 12° C. Anæsthesia is obtained in about 2–5 minutes, but complete muscular relaxation is often absent. Recovery follows a few minutes after the removal of the mask. It is not unpleasant to inhale and generally induces no excitement or other unfavorable symptoms. The pulse is generally slowed, while the respiration is deep. Embley states that in animals the effects are similar to those of chloroform, but that it is less poisonous to the heart, about 19 times as concentrated vapor being necessary to weaken it. The concentration of ethyl chloride vapor necessary to induce cardiac inhibition is four times that of chloroform, and this inhibition is not fatal as the heart muscle is less affected. The vapor may be inhaled in 5–7 per cent. concentration without inducing inhibition in the dog. Nicloux found about 20 mgs. of ethyl chloride per 100 c.c. in the blood in light anæsthesia, from 30 to 150 mgs. in deep anæsthesia and 40–180 at death. A number of fatalities have occurred under its use, about one in three thousand of those anæsthetized. Some major operations have been performed under ethyl chloride, but it is found difficult to maintain a uniform anæsthesia, owing to the rapidity with which consciousness returns. It is often employed to introduce anæsthesia, which is then maintained with ether. Ethyl chloride should not be administered in larger quantities than 4–5 c.c.

Various other members of the fatty series have been introduced as general anæsthetics at different times, but few of them have proved to have any advantage over chloroform and ether, and fatalities have occurred after all of those that have received a wide trial. **Pental**, trimethylethylene ($(CH_3)_2C=CHCH_3$) was introduced for short operations but a number of accidents occurring under it have curtailed its use. It produces anæsthesia before the reflexes disappear or the muscles relax, and not infrequently the jaws are tightly closed after consciousness is lost. In some cases tremor and convulsive attacks have occurred during its administration, but it seems to have very little action on the heart or circulation. **Ethyl Bromide** (C_2H_5Br) has also been used for short operations instead of chloroform, and produces anæsthesia with great rapidity. Consciousness returns quickly after the removal of the mask, but the inhalation is not so pleasant as that of ethyl chloride and patients complain of greater depression and discomfort afterwards. Hennicke found that 10 vol. per cent. of ethyl bromide were necessary to anæsthetize animals within five minutes, and that if this concentration were maintained, death occurred in fifteen minutes, so that it is by no means to be considered a perfectly safe anæsthetic; several deaths have occurred from its use in dentistry. Both pental and ethyl bromide are administered on a mask in the same way as ether. Ethyl bromide must be distinguished from ethylene bromide ($C_2H_4Br_2$) which is a much more dangerous anæsthetic. Ethyl bromide is very liable to decomposition when kept long, and is often furnished in an impure form; it ought to be perfectly colorless, as a yellowish color indicates decomposition, often with the presence of free bromine.

[illegible] (relieving the anxiety to surgeon & patient.

The other members of this series possess no practical importance. It may be mentioned that tetrachloride of carbon (CCl_4) differs from the others in causing convulsions, while perchlorethane (C_2Cl_6) is a crystalline solid and possesses too high a boiling point to be available for inhalation.

Therapeutic Uses.—Anæsthesia is generally induced for the purpose of surgical operations and examinations, and in labor. Until recent years, when it was necessary to perform an operation or manipulation involving much pain, the surgeon had to consider only which of the two general anæsthetics was the better adapted to the case. But the improvements introduced in the methods of inducing local anæsthesia and the reintroduction of nitrous oxide and ethyl chloride as surgical anæsthetics have now enlarged his field of choice, and the further question has to be met whether unconsciousness is desirable, or whether the necessities of the case may not be met by paralyzing sensation at the seat of operation only. The advantages claimed for local anæsthesia will be discussed under cocaine, but the general conditions in which chloroform and ether are to be preferred may be stated shortly (see also nitrous oxide). General anæsthesia is absolutely essential where complete relaxation of the muscles is desired, and where the movements of the patient may imperil the success of the operation. Operations on the abdominal organs and around joints and such others as involve wide and deep incisions will almost certainly continue to be performed under chloroform or ether, although a few such operations have been attempted under cocaine. In many less serious operations it is necessary also to have recourse to the older methods, which allow greater freedom to the surgeon, who is under no apprehension that he may reach a sensitive area and has thus one less source of anxiety than if the anæsthesia were localized. Another argument for the use of general anæsthetics is the effect which the anxiety and the sights and sounds of the operating room may have on a nervous patient even when no actual pain is felt. And a considerable amount of practice is required before complete local anæsthesia can be induced over an extensive field of operation, while the surgeon has often to interrupt his manipulations in order to admit of a fresh area being rendered analgesic. But there is no question that many operations in which ether or chloroform have hitherto been employed, will in the future be performed more often under local anæsthesia or nitrous oxide. In this class may be included most minor operations in which only very short or partial anæsthesia is necessary and in which no complications are to be anticipated. Nitrous oxide and ethyl chloride are scarcely to be regarded as rivals to ether and chloroform in any but minor operations. But in these they have the great advantage that the patient can be dismissed within a few minutes after the operation is completed, while if ether or chloroform is employed complete recovery is only reached after several hours; when the latter are used in minor operations, the discomfort resulting from the anæsthetic may be altogether out of proportion to the actual surgical manipulation.

During labor only the lighter degrees of anæsthesia are necessary, In labor only I. Remote danger to foetus if II or IV. A few whiffs stops strychnine & tetanic convulsions - little loss of consciousness. Erotic dreams.

the object being to dull the pain without lessening to any marked extent the reflex irritability of the spinal cord, and accidents are extremely rare in this use of anæsthetics, although the common statement that they are unknown is incorrect. Some cases have been recorded in which it is believed that chloroform was fatal to the child and not to the mother, but it is, of course, impossible to state with certainty that the anæsthetic was the cause of death. If too deep anæsthesia is produced, however, it is quite conceivable that the labor may be prolonged, or the blood-pressure so reduced as to lead to an imperfect exchange of gases in the placenta and thus to the death of the infant; or as another explanation it might be suggested that the irritability of the respiratory centre of the child may be so reduced that it fails to react when the placental circulation is interrupted.

Anæsthetics are also employed in cases of extreme irritability of the central nervous system, as in strychnine poisoning, tetanus or other convulsive affections. In order to reduce these, it is unnecessary to produce deep anæsthesia, a few whiffs of chloroform being generally sufficient to produce quiet, often without ~~affecting the consciousness to~~ any marked extent. In cases of very acute pain, chloroform or ether may be used, but as a general rule morphine or opium is preferable, as the action lasts much longer and the administration is much more convenient.

During the stage of excitement of anæsthesia, the dreams of the patient sometimes assume an erotic character, and charges of criminal assault have been repeatedly brought against surgeons by women whom they had anæsthetized. It is, therefore, advisable to give chloroform to women only in the presence of a third person.

The local action of chloroform and ether on the stomach and skin is entirely independent of their action as anæsthetics, and will be discussed separately (see page 182).

PREPARATIONS.

U. S. P.—CHLOROFORMUM, a liquid containing 99–99.4% by weight of absolute chloroform ($CHCl_3$) and 0.6–1% of alcohol. $CHCl_3$

ÆTHER, ether, a liquid composed of about 96% by weight of absolute ether or ethyl oxide ($(C_2H_5)_2O$) and about 4% of alcohol containing a little water. $(C_2H_5)_2O$

ÆTHYLIS CHLORIDUM, ethyl chloride (C_2H_5Cl), an extremely volatile liquid boiling at 12.5–13° C. (about 55° F.).

B. P.—CHLOROFORMUM, chloroform ($CHCl_3$), must have a specific gravity of 1.490–1.495, that is, must contain 99% of absolute chloroform.

Æther, ether, or sulphuric ether, a volatile liquid prepared from alcohol and containing not less than 92% by volume of pure ether or ethyl oxide ($(C_2H_5)_2O$).

ÆTHER PURIFICATUS, ether freed from most of the alcohol or water, and of 0.720–0.722 specific gravity.

Chloroform is ordinarily formed by the action of chlorine on alcohol, the chlorine being added in the form of chlorinated lime. The crude drug is purified by repeated washing with water and sulphuric acid, and dried over calcium chloride. The fatalities following its use have frequently been ascribed to impurities, and a certain demand has arisen for a purer article than that required by the pharmacopœias. Another method of preparation [illegible] color. In air → [illegible] - [illegible] kept in dark place. Chlor + Δ = CCl2O - phosgen - very irrit. Boils 60°-62°C. Sweet & pleasant odor. Ether - no impurities of importance. 36-37°C. Kept cool as very inflammable when mixed with air.

has therefore been introduced, the decomposition of chloral by soda (*Chloroformum e Chloral præparatum*). Other pure forms are prepared from ordinary chloroform by crystallizing it by cold (Pictet), or by forming a compound with salicylid and decomposing it again by slight heat, *Chloroform* (*Anschutz*) or *Chloroform* (*Salicylid*).

The impurities of chloroform are due partly to imperfect manufacture and partly to decomposition. Along with the chloroform ~~there distils~~ over a small quantity of heavy oily fluid, which may be isolated by Pictet's method, but whose composition is entirely unknown. DuBois-Reymond found that this fluid acted more strongly on the heart than pure chloroform, but it is very questionable whether the minute quantities inhaled in ordinary anæsthesia produce effects of any importance, and, on the other hand, it is quite certain that the use of absolutely pure chloroform does not prevent accidents. Chloroform undergoes decomposition when exposed to light and air, hydrochloric acid and chlorine being ~~set free in small~~ quantity. These can affect the course of anæsthesia only through their local irritant action, but if present in sufficient quantity may cause the respiration to be more irregular than usual in the earlier stages; the chloroform used for anæsthetic purposes ought, therefore, to be kept in a dark place or in colored bottles. Another decomposition occurs when chloroform is evaporated in the neighborhood of a large flame, such as that from gas or lamps, and hydrochloric acid and phosgen (CCl_2O) are formed, the latter being a gas with exceedingly irritant properties.

Chloroform is a heavy volatile fluid, of characteristic pleasant odor and hot sweetish taste. Its specific gravity is 1.490 (U. S. P.) and 1.490–1.495 (B. P.), and ~~it boils at 60–62° C.~~ A number of tests are given for impurities, but those of importance can generally be detected by the odor, especially if some chloroform be allowed to evaporate in a watch-glass, when the last drop ought to have no irritant effect when inhaled. Chlorine and hydrochloric acid may be tested for by shaking the chloroform with distilled water, and testing the latter with potassium iodide and starch and with silver nitrate. The water ought to give no acid reaction to litmus. If left in contact with concentrated sulphuric acid, chloroform should not become darker within one hour, as this indicates the presence of some foreign unstable body. The other impurities require complicated chemical processes for their detection.

Ether is prepared by the action of sulphuric acid on alcohol, and is subsequently purified by washing with water and alkalies. It seldom contains impurities of importance. Æther (B. P.) is unsuited for anæsthesia, and, ~~in fact, is entirely~~ superfluous. Æther purificatus (B. P.) and Æther (U. S. P.) are practically identical and are the forms intended for inhalation. Ether is a very volatile fluid, ~~of a suffocating,~~ irritant odor and bitter taste. Its specific gravity is 0.725–0.728 (U. S. P.), and 0.720–0.722 (B. P.), and its boiling point is 36–37° C. It evaporates very rapidly in the air and should leave no ~~foreign odor and no residue~~. It should not color litmus paper, nor be colored within an hour when shaken with potassium hydrate solution. Ether vapor is exceedingly inflammable when mixed with air, and it should therefore be kept in a cool place, away from gas flames or lamps.

Local Action and Uses.

In addition to their use as anæsthetics, chloroform and ether are sometimes prescribed for the same purposes as the volatile oils. Chloroform has a hot, sweetish taste, while ether is bitter and suffocating in the mouth; a sensation of heat and often of pain in the stomach follows when they are swallowed, and chloroform may cause gastric irritation and catarrh when given undiluted. The movements

Locally — carminatives · chlor water give gi. catarrh · Chlor liniment · (Counter-irritant) Action same as vol oils · Spirits aeth · comp 2-4 cc. Spirit of ether & ether (much alc) subcut · for shock & collapse · Ether spray on skin for minor surgery.

of the stomach are accelerated, and Batelli states that a certain amount of shortening of the muscular fibres occurs. The whole effect is similar to that produced by the volatile oils, but absorption probably takes place more rapidly. On the skin, ether evaporates too rapidly to cause much irritation, but chloroform is ~~occasionally~~ used as a rubefacient in the form of a liniment.

PREPARATIONS.

The pure substances may be administered by the mouth, but more frequently other preparations are prescribed.

Chloroform, 0.5–1 c.c. (8–15 mins.).

Æther, 0.5–1 c.c. (8–15 mins.).

0.5-1 cc

SPIRITUS ÆTHERIS (U. S. P., B. P.), 2–5 c.c. (30–90 m.).

SPIRITUS ÆTHERIS COMPOSITUS (U. S. P., B. P.) (Hoffmann's Anodyne) contains a number of esters of ethyl and other substances known as "ethereal oil," together with ether and alcohol, 2–4 c.c. (½–1 fl. dr.).

2-4 cc

SPIRITUS CHLOROFORMI (U. S. P., B. P.), 1–4 c.c. (20–60 min.) (5–20 m. for repeated doses, B. P.).

Emulsum Chloroformi (U. S. P.), 8 c.c. (2 fl. drs.).

Aqua Chloroformi (U. S. P., B. P.).

Linimentum Chloroformi (U. S. P., B. P.).

Tinctura Chloroformi et Morphinæ Composita (B. P.) contains one per cent. of morphine hydrochlorate, chloroform, prussic acid, cannabis indica, capsicum and oil of peppermint, and represents the patented medicine "chlorodyne." Dose 5–15 m. It is used as a soporific (see morphine).

Therapeutic Uses.—These preparations are used for the same purposes as the corresponding preparations of the volatile oils. Thus the spirits and emulsion may be prescribed as carminatives or in colic, while the liniment is used as a counter-irritant. Chloroform water is an antiseptic of considerable power, but is too volatile for surgical use.

Spirits of ether and ether itself are often given internally or subcutaneously in cases of shock or sudden collapse in the same way as brandy or whiskey, though Elfstrand states that ether injected hypodermically has no effect on the heart or blood-pressure; spirits of ether contains a much larger percentage of alcohol than ordinary whiskey. Both ether and chloroform, but more especially the latter, have been used internally for tapeworm with success. There is always some danger, however, that, besides destroying the parasite, they may cause irritation and lasting injury to the intestinal wall.

Hoffmann's anodyne is a favorite carminative, and is often added to other drugs to lend them an agreeable odor and taste. It is also used in dilution as a stimulant in the same indefinite way as wine and spirits, and its large percentage of alcohol, together with the bouquet given it by the various esters present, entitle it to be ranked among the alcoholic preparations.

Both spirits of ether are used occasionally in expectorant mixtures and are believed to increase the bronchial secretion.

Ether evaporates very rapidly and leaves a sensation of cold, and when thrown on the skin in a fine spray it produces sufficient cold to numb sensation in the part and allow of minor surgical operations

Ethyl & methyl chloride sometimes as spray for evaporation.

(see uses of cocaine). Instead of ether still more volatile substances, such as ethyl chloride (boiling point 12.5° C.) and methyl chloride (boiling point —23° C.) have been introduced. The latter is supplied in pressure cylinders, and is allowed to escape against the skin, while the others are thrown against it by pumping air through them. The local anæsthesia produced bears no relation to their action when inhaled, but is due simply to the cold produced by their evaporation. The vessels of the part contract, and the absence of blood and hardness of the tissues facilitate some operations, but the subsequent reaction is liable to produce considerable soakage of blood from the wound. The cold elicited ought not to be great enough to actually freeze the tissues, otherwise the healing may be slow. The intense cold is often quite as painful as the operation itself would be without any anæsthetic.

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N_2O laughing gas. drumming, staggering, ~~warmth~~ laughter, warmth, lessened perception. Pure N_2O: passes at once thru these stages to unconsciousness. When cyanosis commences remove mask or cessation of resp. anaesthesia lasts 30–60 sec. Recovery & no after effects

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3. Nitrous Oxide.

The oldest of the anæsthetics, nitrous oxide, N_2O, does not belong to the methane series, but may be discussed at this point.

Symptoms.—When a mixture of nitrous oxide and air is inhaled for a few seconds, a condition resembling alcoholic intoxication is produced, with much hilarity and laughter, so that the oxide is known popularly as "laughing gas." Even at this point a certain amount of anæsthesia is obtained, and it was the observation that persons falling during this stage did not complain of pain that first suggested to Wells the anæsthetic properties of the gas. Davy had noted these forty years previously, but his suggestion that nitrous oxide might be used in surgical operations passed unnoticed.

The inhalation of a mixture of nitrous oxide, 4 parts, and oxygen, 1 part, causes after a few seconds a rushing, drumming, hammering in the ears, indistinct sight, and a feeling of warmth and comfort. Why? The movements become exaggerated and uncertain, the gait is staggering, and the body sways from side to side. The patient seems brighter and more lively, and often bursts into laughter. Somewhat later a feeling of drowsiness may come on, but this is not constant; the sensibility to pain is much less acute than normally, but no complete anæsthesia is produced by this mixture of gases; the sense of touch is comparatively little altered, and total unconsciousness never results. The pupil is generally slightly dilated, the face flushed, and the pulse somewhat accelerated.

When pure nitrous oxide is inhaled without the admixture of oxygen, the patient passes almost instantaneously through the symptoms already described, but then loses consciousness completely; the face is cyanotic, the respiration becomes stertorous and dyspnœic and ceases after a weak convulsion, while the heart continues to beat for some time afterwards. If the mask through which the patient has been inhaling the gas is removed when the cyanosis becomes marked, very complete anæsthesia lasts for 30–60 seconds, and the patient then recovers within a few minutes and suffers from no after-effects whatever. No prolonged anæsthesia can be produced, however, as the respiration becomes endangered if the mask be kept on longer than the beginning of the cyanotic stage.

Action.—Nitrous oxide supports combustion outside the body, for if a glowing splinter of wood be held in it, it bursts into flame exactly as if it were immersed in oxygen. It was accordingly believed at one time that nitrous oxide supported the combustion of the living tissues in the same way as oxygen, but this has been disproved, for as far as the metabolism of protoplasm is concerned, nitrous oxide behaves in

[illegible]
inhaled (no oxyhaemoglobin) Undoubtedly, N_2O has spec. narcotic power, other than cerebral anaemia. Indifferent to other tissues

the same way as any other indifferent gas, such as hydrogen or nitrogen; that is, the tissues exposed to it suffer from asphyxia owing to the oxygen of the air being excluded. Thus, plants do not grow in an atmosphere of nitrous oxide and seeds do not germinate. Animals die after inhaling nitrous oxide in almost the same time as after hydrogen or nitrogen, and at death the spectrum of the blood shows no oxyhæmoglobin to be present, the tissues having used up all the available oxygen. Nitrous oxide, therefore, does not support combustion in the animal body, the nitrogen is not split off from the oxygen as it is when the oxide is exposed to high temperatures outside the body.

Another question is whether nitrous oxide behaves only as an indifferent gas in the body, or whether it has not some special effect on the central nervous system, although in the rest of the tissues it acts only by excluding the oxygen. The earlier workers in this field held that it affected the central nervous system only by cutting off its supply of oxygen, but this has been shown to be erroneous, for nitrous oxide acts as a depressant to the central nervous system by virtue of its molecular form just as chloroform or ether does. This has been shown in a variety of ways; thus, if it were a perfectly indifferent body no more effect would be produced by it when mixed with one fourth of its volume of oxygen than by air, which consists of 1 part of oxygen and 4 parts of an indifferent gas, nitrogen. But 80 per cent. nitrous oxide has definite effects on the behavior of animals, as has been mentioned, and even 73 per cent. produces some slowing of the respiration. The narcotic action was demonstrated very clearly by Paul Bert in a series of experiments on man and animals. He noted that only imperfect anæsthesia was produced by 80 per cent. nitrous oxide, while the pure gas produced asphyxia. The problem was to introduce as much gas into the blood as would pass in under pure nitrous oxide, and at the same time to supply sufficient oxygen to prevent asphyxia. The absorption of nitrous oxide depends upon its partial pressure in the lungs, as it is simply dissolved in the blood without forming any real combination with it, and the quantity absorbed by the blood may be augmented by increasing the barometric pressure. Bert, therefore, administered a mixture of 80 parts nitrous oxide and 20 parts oxygen to animals in a glass case in which the pressure was raised one-fourth above the ordinary atmospheric pressure. The absorption of the nitrous oxide was the same as if the animal had breathed the pure gas at the ordinary air pressure, and at the same time as much oxygen was absorbed as in ordinary air. The result was a complete anæsthesia without asphyxia, which could be maintained for three days without injury to the animal (Martin). Kemp has recently shown that mixtures of oxygen and nitrous oxide can be inhaled for some time and produce anæsthesia, which passes off at once when nitrogen is substituted for nitrous oxide. He has further investigated the blood gases during nitrous oxide anæsthesia, and finds that the oxygen contained in the blood at the deepest stage of anæsthesia is quite sufficient to [illegible] failure from direct action on center of lack of O, Excitement due to lessened control. Asphyxia, [illegible]. Heart only affected by lack of O

maintain life and consciousness were no nitrous oxide present. Again Goltstein found that frogs were narcotized in five and one-half minutes in an atmosphere of nitrous oxide, in one and one-quarter hours in hydrogen, and showed that the narcosis and death in mammals from nitrous oxide differed in several details from that under indifferent gases. There can, therefore, be no doubt that nitrous oxide has distinct effects on the central nervous system, although it is indifferent to the other tissues. A further question arises, whether the anæsthesia produced by it in ordinary use is due to this specific action on the nerve cells alone or to the asphyxia. Wood has shown that even a slight admixture of oxygen (3 per cent.) delays anæsthesia considerably, so that the lack of oxygen appears to aid the direct effects of the anæsthetic. Bert's and Martin's experiments would indicate that death occurs, not from the direct action of the nitrous oxide on the respiratory centre, but from the lack of oxygen, although the depression of the centre is undoubtedly a contributing factor.

The same question arises regarding the action on the nerve cells as has been met with in the members of the methane series, and here again the preliminary excitement may indicate not stimulation of the brain areas, but lessened activity of the functions of control and restraint.

The respiratory centre is depressed when the gas is inhaled in comparatively dilute form, for Zuntz and Goltstein found the breathing slower and deeper after 73 per cent. The respiration ceases somewhat earlier under nitrous oxide than under indifferent gases, which would indicate that the cessation of the breathing is due at any rate in part to the specific depressant action. In asphyxia from nitrous oxide there is less convulsive movement than under hydrogen, owing to the general depression of the nerve cells.

The circulation is little affected by the nitrous oxide directly, the rise in the blood-pressure and slowness of the pulse being due to the asphyxial condition of the blood; the pulse is not so slow as in ordinary asphyxia or in asphyxia from nitrogen or hydrogen, because the inhibitory centre is less capable of activity. The heart is not affected directly, but only by the lack of oxygen.

The blood dissolves more nitrous oxide than water, apparently because it is taken up by the lipoids of the corpuscles in the same way as chloroform. Nicloux found about 40 mgs. in 100 c.c. blood at the beginning of anæsthesia, 50 mgs. in complete anæsthesia, and 60 mgs. when the respiration ceased.

Nitrous oxide is a gas at ordinary temperature and pressure, and is invariably administered by inhalation from a cylinder into which it has been forced under high pressure. The mask generally covers both nose and mouth, and the inhalation is carried on until distinct cyanosis appears, when the anæsthesia is sufficient to allow of short operations, such as those of dentistry. It is much the safest of the anæsthetics, for millions of persons have been subjected to its influence, and only a few cases of death are reported from its use, and several of these do

Very safe [illegible]
Devices (under pressure so that O may be given to maintain [illegible] for maintaining anaesthesia for 1/2 hr. ~~Not~~ complete relaxation: Much gas necessary
80% gas for ~~patients~~ inhalation (alone) in asthma, labor etc

no seem to have been due to the direct action of the gas. Of late years ethyl chloride (see p. 179) has been introduced as a substitute for nitrous oxide, and has supplanted it to a certain extent, as it is more easily administered and the apparatus necessary is much less cumbrous. On the other hand, nitrous oxide is responsible for much fewer accidents. Unfortunately, the anæsthesia cannot be kept up except for a very short time, which is quite insufficient to allow of ordinary operative procedures. A number of attempts have been made to prolong the anæsthesia, of which Bert's was much the most successful. The operator, patient and attendants were enclosed in an air-tight chamber, the air pressure was raised by means of force pumps, and Bert's mixture of oxygen and nitrous oxide was inhaled by the patient. A whole series of major operations were performed in this way, the anæsthesia being complete as long as was desired, and the patient recovering a few minutes after the mask was removed. The only objections to the method were the great expense of the chamber and of pumping the air and the inconvenience attending the whole procedure. Bert, therefore, proposed later to induce anæsthesia by pure nitrous oxide, and then to substitute for it a mixture of oxygen and nitrous oxide, and to keep up the anæsthesia as long as desired by alternating between the pure gas and the mixture. A practical method of carrying out this form of anæsthesia has been devised by Hewitt, whose results have led to a wider trial of diluted nitrous oxide anæsthesia than it has hitherto had. His apparatus consists essentially of two reservoirs, the one containing oxygen, the other nitrous oxide, and of a mixing chamber with a stopcock by which the proportion of oxygen is regulated. A tube leads from the mixing chamber to the mask which must fit closely to the face. The inhalation is commenced with pure nitrous oxide or with a mixture containing only 2 per cent. of oxygen. When anæsthesia is attained the percentage of oxygen is increased to 5–8 per cent. by turning the stopcock, and the symptoms determine the further changes, returning consciousness necessitating a diminution in the oxygen, stertor and cyanosis an increase. This form of anæsthesia is admirably adapted for minor operations and has been maintained in some cases for as long as an hour. The circulation and respiration are less seriously altered than by any other method that induces general anæsthesia, and the return of consciousness is almost immediate. The great drawback to its use is the cumbrous apparatus required and the large amount of gas used, amounting to about 100 gallons for anæsthesia of half an hour. Complete muscular relaxation is seldom attained and this precludes its use in many operations, in which, however, it may be employed at first and then be replaced by chloroform or ether, whose preliminary disagreeable effects are thus avoided. Klikowitsch proposed the use of 80 per cent. nitrous oxide, not for complete anæsthesia, but to relieve pain and spasm in cases of asthma, in labor and similar conditions. The patient could inhale it if necessary without the presence of a medical attendant, and it had the advantage over the other depressants that it need only be inhaled

Asphyxia = high b.p. (aged?) & unimportant diabetes. Accidents give artificial resp.

Narcotics for T + sleep. lasting effect. non-irritant. less rapidly absorbed. Sol in H_2O

Chloral 15–30 gr. – unshakable sleep for 5–8 hrs. Pain, noise awakens

5 [illegible] more [illegible] stupor, lessened pain sense – on waking in 15 hrs.

nausea. headache. vertigo. Exactly like [illegible] – loss of reflexes – Cardiac [illegible]. Then resp failure

when an attack of pain was approaching and that it left no depression afterwards.

The high blood-pressure induced by nitrous oxide asphyxia is sometimes said to be dangerous in elderly persons from their liability to apoplexy, and of the few fatalities under the gas several would seem due rather to this than to the drug directly, but the danger is often overstated, and, in fact, it is a question whether the shock caused by the operation without gas would not be more dangerous than the effects of the gas itself. No such symptoms arise when the nitrous oxide is diluted with oxygen as in Hewitt's method.

Occasionally some glycosuria occurs after the inhalation, not owing to the gas itself, but to the accompanying asphyxia. It is merely temporary and has no practical importance.

The treatment of accidents in anæsthesia under nitrous oxide consists in artificial respiration alone.

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4. Soporifics.—Chloral.

Some twenty years after the introduction of the anæsthetics, a new interest was given to the methane series by the examination of the action of chloral by Liebreich. Henceforth the attention of investigators was diverted from the quest of anæsthetics to that of hypnotics, with the result that a very large number of bodies have since been suggested for this purpose and that a few valuable drugs have been added to therapeutics. These soporifics, or narcotics, have the same general action as the anæsthetics, but are used only to produce the first effects of imperfect consciousness or sleep. The anæsthetics might be used for this purpose were it not for the comparatively short time during which their action persists. Narcotics are required to produce a slight but lasting effect, and for this purpose the gradual absorption ~~from the stomach~~ is better adapted than the rapid absorption and equally rapid elimination by the lungs. The narcotics are, therefore, less volatile than ~~the anæsthetics~~, and ought to be soluble in water and not irritant in the stomach, so as to permit of rapid absorption. Chloral is still the best known and most widely used member of this group.

Symptoms.—Chloral in 15–30 gr. doses produces drowsiness and weariness, which soon pass into a condition resembling natural sleep very closely, from which the patient can be awakened by ordinary

Chloral etc depresses c.n.s. & then paralyzes. Rarely excitement preceding
Sensory or receptive function of brain depressed & motor activity reduced.
No spec. effect on algesic centre (morphine does) so that stimuli as pain
interrupt sleep. Not so in large doses.

means, such as touching, loud sounds, or pain. The respiration and pulse are somewhat slower than in waking moments, but scarcely more so than in natural sleep, and the somewhat narrowed pupil and unaltered excitability of the reflexes are also common to both conditions. As a general rule, the sleep passes off in five to eight hours and leaves no unpleasant results, but sometimes headache, giddiness and confusion are complained of. Occasionally no real sleep is produced by chloral, a condition exactly resembling alcoholic intoxication following its administration and continuing for some time. When larger quantities, *e. g.,* 5 G. (75 grs.), are taken, the sleep is much deeper, the patient cannot be aroused to complete consciousness, the reflexes are distinctly lessened and the sensation of pain is less acute, although no complete anæsthesia is present. The respirations are fewer and the pulse may be slow and somewhat weak. The sleep lasts very much longer (ten to fifteen hours), and nausea, vomiting, headache and confusion often remain after consciousness is regained. In still larger quantities chloral produces a condition resembling exactly the third stage of anæsthesia. The reflexes are entirely absent and no movement is elicited by painful operations, the muscles are completely relaxed, the respiration and pulse are both slow and weak, and eventually asphyxia occurs from paralysis of the respiratory centre. The heart continues to beat for a short time after the breathing ceases.

The first stage is the only one elicited in therapeutics. The use of chloral as an anæsthetic in man would be quite unjustifiable, because it is impossible to adjust the dose accurately enough to allow of complete anæsthesia without danger of respiratory failure.

Action.—The **Central Nervous System** is depressed and eventually completely paralyzed by chloral and its allies. Unlike the anæsthetics and alcohol, however, chloral rarely causes excitement, but this may be due to the facts that the surroundings of the patient are less likely to cause excitement and that the drug itself causes less local irritation. The results of psychological experiments on the effects of small doses of the narcotics seem to indicate that they all depress the sensory or receptive functions of the brain, while its motor activity is much reduced by chloral and sulphonal, but may appear to be actually increased by paraldehyde; this apparent stimulation is analogous to that under alcohol and may be explained by lessened control. The sleep induced by the dulling of the perceptions may be interrupted by more intense stimuli from without. In particular, acute pain may prevent sleep after chloral, which seems to have no specific effects on the algesic areas, such as is possessed by morphine; the sensibility of the skin is also less affected by chloral than by morphine. In larger quantities, however, even very great disturbance of the environment produces no interruption of the sleep, and the reflex response to irritation is very much lowered. The motor areas of the brain cortex are rendered less irritable by chloral, and eventually fail to react to the strongest electrical stimulation. The reflexes of the spinal cord are depressed and finally paralyzed before the failure of the respiration.

Resp. + heart slower as in [illegible] sleep; unless in large doses little effect; then depression of vas. centre & weak aur. contractions etc. In hypertonic sol = irritant. On skin may corrode. Taken up by cells

Hypodermically = rigor. (Spens

The depression of the reflexes is one of the points which serve to differentiate the action of most of the methane series from that of the alkaloidal narcotics, such as morphine. The last part of the central nervous system to be attacked is the medulla oblongata, for although the respiration is somewhat slower and shallower after small quantities, it is scarcely more affected than in ordinary sleep, and Loewy found that both the excitability of the centre and the volume of the inspired air were very similar in the two conditions. As the dose is increased, however, the respiration becomes very slow and weak, and finally ceases from paralysis of the centre.

The heart is somewhat slower after chloral in moderate doses, but scarcely more so than in natural sleep. There is often some flushing of the face and head from some obscure central action, but the blood-pressure is little affected except by large quantities, which reduce it considerably and at the same time cause marked slowness of the pulse. The depression of the blood-pressure is caused in part by paresis of the vasomotor centre, in part by the effects on the cardiac muscle, and possibly in part by a direct action on the muscular walls of the vessels. It is much more evident in poisoning with chloral than with the other soporifics, this group presenting the same differences in this respect as the general anæsthetics. In both cases it is to be noted that the molecule containing chlorine has the more powerful action on the circulation. In chloral poisoning, as in chloroform, the effect on the heart is so great as to give rise to anxiety quite apart from the condition of the respiration, and in fact some cases of poisoning are said to have terminated with failure of the pulse before the respiration, though this is unlikely. The extreme weakness of the heart may, however, aid the direct action of the drug in its effects on the respiratory centre. The alterations in the heart are similar to those produced by chloroform, the auricular contractions becoming weak earlier than the ventricular, and some dilatation occurring in both chambers. It may be added that only very large quantities of chloral affect the heart, and that there is no reason to suppose that in therapeutic doses it has any effect whatever on it or on the arterial tension.

Locally, chloral has an irritant action when applied in concentrated solution and this leads occasionally to nausea and vomiting when it is prescribed with insufficient fluid. This irritant action induces redness and even vesication when chloral is applied to the skin; it is said to corrode when applied to unprotected surfaces, and certainly possesses antiseptic properties like chloroform. It is rapidly absorbed when given by the mouth and is carried to the central nervous system where it is taken up by the cells until they contain more than the blood corpuscles or the cells of other organs, such as the liver. Liebreich introduced chloral as a hypnotic in the belief that it was decomposed in the blood and chloroform liberated, but this has been shown to be erroneous, no chloroform being found in the blood or expired air after chloral. Chloral has no action on muscle or nerve in the living animal, but when it is applied to the exposed nerve it first irritates

Dilated skin vessels + lessened movement = fall in temp.
Urine's acidity increased, N output up, combustion not complete
(urochloralic acid (reduces Fehling))
Circ. & metabolism little affected by by non Cl containing drugs

Paraldehyde Sulphonal [illegible] [illegible] center — N not up. Parald. like alcohol, but no II stage. Sulph. insol. H2O, effect slow & prolonged [illegible] effect; with both [illegible] not fatal, prolonged unconsciousness; but less danger than chloral.

and later paralyzes it, and injected directly into the artery of a muscle it causes immediate rigor. The temperature falls after the administration of chloral from the lessened muscular movement, and perhaps from the increased output of heat through the dilated skin vessels.

The effects of chloral on the tissue-change have been recently investigated and found to correspond very closely to those of chloroform. Thus fatty degeneration of various organs has been produced by the prolonged administration of chloral and of chloralamide, and the increase in the nitrogen, phosphates and sulphur, especially of the unoxidized sulphur, in the urine points to augmented destruction of the proteins of the body, together with imperfect oxidation. The acidity of the urine is much increased by the presence of urochloralic acid. The excessive production of this acid in the tissues has been said to be the cause of the alterations in the metabolism, and as a matter of fact Kleine has found that the addition of alkaline carbonates to the food prevents these effects of chloral. Chloral was formerly supposed to lead to glycosuria, but this has been shown to be erroneous, the reducing substance in the urine being urochloralic acid, and not sugar. In addition to this effect on the tissues generally, less oxygen is absorbed and less carbonic acid excreted owing to the diminished muscular movement.

Chloral is reduced in the tissues to trichlorethyl alcohol (CCl_3CH_2-OH), which combines with glycuronic acid to form urochloralic acid, and is excreted in this form in the urine. Some escapes by the kidneys unchanged, however, and some is thrown into the stomach, and this may account for the nausea and discomfort felt after awaking in some cases.

The other hypnotics of this series, with the exception of chloralose, correspond exactly with chloral as far as their action on the central nervous system is concerned. The chief difference in their effects is seen in the circulation and metabolism, which are comparatively little affected by those which do not possess substituted chlorine atoms.

Paraldehyde and **Sulphonal** do not affect the heart directly, although they may cause a slight acceleration of the pulse through their depressant action on the inhibitory centre. They lessen the metabolism through their action on the central nervous system, but produce no such marked alteration in the protein decomposition as follows the administration of chloral. Paraldehyde resembles alcohol in its effects, though it is a much more powerful narcotic and rarely induces any symptoms of excitement. Very large quantities of sulphonal and paraldehyde have been taken without fatal results, and in fact without any more serious consequences than prolonged unconsciousness, so that they are much safer narcotics than chloral. Paraldehyde, however, has a most unpleasant odor and a hot, burning taste, which renders its administration somewhat difficult. In addition it is excreted in part by the lungs, though mainly in the urine, and the odor remains in the breath for some time after the patient awakens. The insolubility of sulphonal in water renders its absorption very slow and

Following [illegible] sometimes haematoporphyrin (from haemoglobin) - Anaemia, death
Bad effect on heart when used over long periods
Veronal (5-10 grs) - Specific on CNS. natural sleep. Rarely followed by drowsiness

imperfect, and sleep is therefore late in following its administration, while, on the other hand, depression, drowsiness and lack of energy are often complained of the day after. There is some evidence that sulphonal exercises a deleterious effect on the liver, for the relation of urea to the total nitrogen of the urine is changed and the metabolism of the purine bodies is also affected.

The use of sulphonal, especially when prolonged, has led in some cases to a series of symptoms, the most characteristic of which is the appearance in the urine of a reddish-brown pigment, hæmatoporphyrin, an iron-free product of the decomposition of hæmoglobin. This occurs most frequently in anæmic women, and is accompanied by constipation, pain in the stomach region and vomiting, weakness and ataxia, confusion and partial paralysis, and eventually by suppression of the urine or by collapse and death.[1] Hæmatoporphyrin occurs in traces in the urine of the rabbit normally and in much larger quantities after the animal has been treated with sulphonal (Neubauer). Its appearance in the human urine appears due to some obscure change in the liver, and not to derangement of the renal functions, although in one case the kidneys were found to be diseased; in animals the prolonged administration of sulphonal often causes albumin and casts in the urine, while hemorrhages in the kidneys have been produced in them by the administration of only a few doses. The amount of hæmatoporphyrin in the urine is sometimes very large; in one case Tyson and Croftan found that the quantity passed in one day indicated the destruction of one-seventeenth of the total hæmoglobin of the body. Very large doses of sulphonal are said to produce convulsive movements in animals, while ordinary ones cause sleep and subsequent drowsiness. Sulphonal is decomposed in the body and is excreted largely as ethylsulphonic acid in the urine, in which traces of the unchanged substance have also been found. The decomposition is a slow process, however, for Kast found sulphonal in the blood many hours after its administration. The ethylsulphonic acid seems to have no action whatever in itself, so that the narcosis is due to the unchanged molecule of sulphonal.

Sulphonal seems to have some deleterious action on the heart when used for long periods, and is a much less certain hypnotic in cases of cardiac disease than in other conditions.

Veronal,[2] one of the most recently introduced hypnotics, seems to be devoid of action except on the central nervous system, and thus approaches the ideal more closely than any of the others. In small doses (5–10 grs.) it induces natural sleep without subsequent depression, and larger quantities deepen and lengthen the unconsciousness without other organs than the central nervous system being involved, though the patient may complain of lethargy and drowsiness subsequently. Fatal poisoning has occurred from very large quantities (*e. g.*, 150

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[1] Occasionally the hæmatoporphyrin appears several days after a single dose of sulphonal or its allies, sometimes after an interval of one or two weeks.

[2] The chemical formulæ of these bodies is discussed on pages 128 and 129.

Trional & Tetronal just like sulphonal:
With me = sleep with no other effects - but fails in some cases!

grs.), the sleep passing into coma, ending in respiratory failure. About 70 per cent. has been recovered unchanged from the urine, the rest apparently undergoing oxidation in the tissues. It acts as a hypnotic in smaller quantities than any of the others of this series.

Butylchloral, or **Crotonchloral**, was said by Liebreich to possess a specific analgesic or anæsthetic action on the nerves of the face and head, but this has been shown to be incorrect by v. Mering, and, as its effects are identical with those of chloral in almost all respects, crotonchloral seems entirely superfluous.

Chloralamide, or chloralformamide, has been introduced in the hope that the ~~stimulant~~ action of the formamide, which is formed by its decomposition, would counteract the depression of the circulation caused by chloral alone. From blood-pressure experiments it would seem that chloralamide fulfils those expectations, and has little or no action on the circulation except in poisonous doses. It is said to be less irritant than chloral in the stomach, but to be somewhat slower and less certain in its effects. Chloral is formed by its decomposition in the body, and is excreted as urochloralic acid, and fatty degeneration has been observed after its prolonged administration. On ~~the whole it would seem~~ to possess the cerebral action of chloral, without producing its effects on the circulation.

Amylene Hydrate, or dimethylethylcarbinol, has been advised as a hypnotic, and is more closely allied to paraldehyde in its effects than to any of the others. It is twice or thrice as powerful a hypnotic as paraldehyde, however, while it is only one-half as strong as chloral. It is said to depress the heart more than paraldehyde, but less than chloral, and to produce excitement and convulsions in the carnivora, but not in the herbivora. Even in man, it causes excitement more frequently than most other soporifics, and Harnack and Meyer state that it first stimulates and then depresses the respiratory centre as well as other parts of the central nervous system, and that it induces a very marked fall in the temperature. The cardiac and voluntary muscle is first increased in efficiency and then depressed. It has little or no effect on the general metabolism, and is excreted in the urine in combination with glycuronic acid in the rabbit, but is exhaled by the lungs for the most part by the dog and possibly by man. It is less certain in its action than chloral but has not received so wide a trial as it would seem to merit. A combination of chloral and amylene hydrate has been introduced under the name of **Dormiol**, but offers no advantages over chloral.

Trional and **Tetronal** are very similar to sulphonal in their chemical structure, and have practically identical results with it in therapeutics, although their action on animals is somewhat more powerful. In some cases of treatment with trional hæmatoporphyrin has been found in the urine.

Urethane would possess all the advantages of the others with none of their disadvantages were not its effect on man much weaker and less constant. In many cases it is an almost perfect hypnotic, easily taken in solution, producing light sleep with no after-effects, but in others it seems to have little or no hypnotic effect. It is oxidized in the body to urea. **Hedonal** appears to have a greater hypnotic effect than urethane, but also fails to induce sleep in a considerable proportion of cases. It is followed by no after-effects and is oxidized in the body in the same way as urethane.

Chloralose acts much more like morphine than like chloral, depressing the psychical functions, while increasing the reflexes until convulsions resembling those of strychnine may be produced. The heart is comparatively little affected, and the respiration remains strong unless very large doses are given. In man it induces sleep, which is sometimes attended by distinctly exaggerated reflexes however, especially when large doses are given.

Bromoform has anæsthetic properties like chloroform, but is not volatile

Bromoform used in whooping cough - may cause fatty degen + other [illegible]. Chloretone - like chloral - less irritant + less circ depression. Also as a local anaesthetic. Are interchangeable tolerance in these groups, also with alcohol. Skin eruptions. Habit - depression, cachexia, gi + mental disturb. Chl-hyd - 5-25 - diluted in syrup. Too irritant for hypo

enough for inhalation. Of late years it has been used internally in whooping-cough, and in this relation it is important to remember that it gives rise to fatty degeneration when taken continuously. A number of cases of alarming poisoning in children have been recorded from its use. It has also been used occasionally in insomnia.

Bromal (CBr_3COH) differs in several respects from chloral in its action. In animals its injection is followed by restlessness and excitement, and then by stupor, which is often accompanied by dyspnœa, and ends in failure of the respiration, or in convulsions. The pupil is much contracted, and profuse salivation is observed. It acts on the heart like chloral but is much more poisonous, and is scarcely used in therapeutics.

Chloretone resembles chloral in most respects, but is less liable to irritate the stomach and does not appear to depress the circulation to the same extent. Very large doses have been swallowed without producing any untoward symptoms, but the hypnotic effect is obtained by the use of smaller doses than are necessary in the case of chloral. Like chloral, chloretone has some virtues as an antiseptic, and in addition it paralyzes the terminations of the sensory nerves when it is applied locally and has proved of value as a local anæsthetic.

Neuronal and **Isopral** have been introduced so recently that little opportunity has been afforded for their study. Animal experiments indicate their possessing a stronger hypnotic action than chloral, and satisfactory results are reported in the cases in which they have been used in therapeutics. The presence of chlorine in the molecule of isopral suggests that it may have some deleterious action on the circulation and metabolism, and the presence of bromine in neuronal is also to be regarded as a drawback. Isopral resembles chloretone in possessing some local anæsthetic power.

Tolerance is soon acquired for each of these drugs, and when it is developed for one, large doses of any of the others are required in order to produce sleep. Tolerance for alcohol also involves the use of larger quantities of the hypnotics, and in fact often leads to the complete failure of any except the most powerful.

Not infrequently the hypnotics lead to skin eruptions, especially when used for some time. These assume various forms, the most common being of the erythema order, but among others urticaria, purpura, papular eruptions and blisters occur.

Habit.—Prolonged abuse of chloral leads to a condition somewhat resembling that seen in chronic alcoholism or morphinism, and marked by general depression and cachexia, with impairment of the mental powers, digestive disturbance and exanthemata. The sudden withdrawal of the drug in these cases has sometimes led to symptoms resembling those of delirium tremens, which are especially dangerous here owing to the fatty degeneration of the heart which may be present.

A few cases of sulphonal habit have also been reported.

PREPARATIONS.

CHLORALUM HYDRATUM (U. S. P.), CHLORAL HYDRAS (B. P.) ($CCl_3CH(OH)_2$ or ($CCl_3COH + H_2O$), a crystalline solid, of a characteristic fruity odor, and hot, acrid taste, readily soluble in water, alcohol, ether and oils, is almost invariably prescribed in dilute solution in syrup. Its deliquescent properties preclude its use in most of the solid preparations, and its irritant effects contraindicate hypodermic injection. Dose, 0.5–2 G. (10–30 grs.), which may be repeated if necessary, in one or two hours. 5 - 25

Sulphonal 1ʒ in hot water or milk - no confusion following.

SYRUPUS CHLORAL (B. P.), ½–2 fl. drs. (one drachm contains 10 grains of chloral).

1-4 cc PARALDEHYDUM (U. S. P., B. P.) ($C_6H_{12}O_3$), a colorless fluid of strong, characteristic odor and burning taste. It may be prescribed in brandy and water, or in water up to 10%, or in capsules. Dose, 1–4 c.c. (15–60 m.).

1ʒ SULPHONAL (B. P.), SULPHONMETHANUM (U. S. P.) ($(CH_3)_2C(SO_2C_2H_5)_2$), a crystalline powder, without taste or odor. It may be prescribed in powder form to be taken one to two hours before retiring, but is soluble in hot water or milk, and when given in solution acts more rapidly and leaves no confusion afterward. It is prescribed in doses of 1 G. (15 grs.).

Sulphonethylmethanum (U. S. P.), *trional* ($CH_3 \cdot C_2H_5 \cdot C \cdot (SO_2C_2H_5)_2$) resembles sulphonal, but is more soluble and has a bitter taste. Dose, 1 G. (15 grs.).

Butylchloral Hydras (B. P.), or Croton chloral ($CH_3CHClCCl_2CH(OH)_2$), resembles chloral and is prescribed in the same way, but generally in smaller doses—0.3–1 G. (5–15 grs.).

Æthylis Carbamas (U. S. P.), urethane ($CO \cdot OC_2H_5 \cdot NH_2$), colorless crystals, odorless, with a cool, saline taste, very soluble in water, alcohol, and ether. Dose, 1–5 G. (15–75 grs.). U. S. P. 1 G. (15 grs.).

Bromoformum (U. S. P.) ($CHBr_3$), a heavy, transparent, colorless liquid with an ethereal odor and a taste like that of chloroform, very little soluble in water, but readily soluble in alcohol. Dose, 0.2 c.c. (3 mins.).

Chloralformamidum (U. S. P.), or chloralamide ($CCl_3CHOHNH \cdot COH$), a white crystalline powder with a faintly bitter taste; prescribed in powder or in solution in water or spirit. Dose, 1 G. (15 grs.).

Unofficial.

Tetronal resembles sulphonal closely, and may be prescribed in the same dose and form.

Amyleni Hydras ($(CH_3)_2COHCH_2CH_3$), a colorless liquid of pungent taste, and of an odor somewhat resembling camphor. It may be prescribed in capsules, or up to 10% in water flavored with liquorice extract. Dose, 3–5 c.c. (40–80 mins.).

2ʒ *Hedonal,* a crystalline powder with a taste resembling that of menthol, very slightly soluble in water. Dose, 2 G. (30 grs.) in powder or tablets.

Chloretone ($CCl_3C(CH_3)_2OH$), colorless crystals with a strong camphoraceous odor, slightly soluble in water, very soluble in alcohol; it may be prescribed in aqueous solution (about 1 per cent.) or, better, in tablets. Dose, 0.3–1 G. (5–15 grs.).

3-6ʒ *Veronal* ($(C_2H_5)_2C(CONH)_2CO$), colorless crystals with a faint bitter taste, soluble in 145 parts of water; prescribed in powders or tablets, to be dissolved in warm water or milk. Dose, 0.3–0.6 G. (5–10 grs.). A weak combination of veronal and sodium has recently been recommended as being more soluble than veronal itself and thus more easily prescribed in solution.

Neuronal ($(C_2H_5)_2BrC \cdot CONH_2$), crystals with a bitter taste resembling that of menthol, soluble in 115 parts of water; prescribed in the same way as veronal in doses of 0.5–2.0 G. (5–30 grs.).

Isopral ($C_2H_3Cl_3CHOH$), white crystals with a camphoraceous odor and aromatic biting taste, soluble in 30 parts of water; prescribed in doses of 0.5–0.75 G. (5–8 grs.).

Therapeutic Uses.—These drugs are chiefly used to produce rest and sleep in cases of insomnia and in almost every form of nervous excitement. Until the discovery of the therapeutic value of chloral, opium was used in most of these cases, and when sleeplessness is due to pain it is still preferable to the more modern remedies, which have comparatively slight influence on acute pain, except in very large doses.

where pain use opium series. In delirium, mania & convulsions, esp where of spinal reflex origin — Strych (chlor & chlorof). tetanus asthma etc. In insomnia to insanity. If fatty degen give non-Cl, paraldeh. sulph., hedonal & veronal. Chloral harmless in other heart cond. Given with opium or bromides = very good sleep with less dose of each. Also opium etc. & bromides & cannabis indica are also narcotics. Chloral good tho expensive antiseptic & counter-irritant. Acute poisoning lavage. stimulants art. resp. hot packs. habit — withdraw slowly.

But in delirium, mania and convulsions of various kinds, their action on the nerve centres is preferable to that of opium, especially where these convulsions are of spinal origin or of a reflex nature; thus, in strychnine poisoning and in tetanus, chloral is of great value, although in the former it may have to be reinforced by chloroform during the convulsions. In delirium from fever or from uræmic intoxication and similar causes, comparatively small doses often produce most satisfactory results, and in various spasmodic affections, such as cough, asthma and choreic movements, it is exceedingly useful. Chloral has also been advised to lessen the pains of labor.

Most of the soporifics have been used more or less extensively as hypnotics in simple insomnia and in insanity, but when the disturbance assumes a more violent character there is a disposition to return to the use of chloral, as at once the speediest and surest remedy of the whole group. When there is any reason to suspect fatty degeneration of the heart, however, some hypnotic which does not contain chlorine ought to be substituted for it, and paraldehyde, sulphonal, hedonal and veronal have been introduced in succession to supply the need. In other forms of heart disease, chloral may be used without danger and is often of great value as a hypnotic; the dread of its affecting the heart deleteriously in ordinary doses is quite unfounded. Chloral is often prescribed along with opium, and, when thus combined, smaller quantities of each drug are required than would be necessary if either were prescribed alone, and the sleep following is very deep and restful. It is also used very often to reinforce the action of the bromides.

Other Narcotics which for some purposes may be substituted for the members of the chloral group are alcohol, opium and its alkaloids, bromides, hyoscine and cannabis indica.

Chloral has been used externally as a counter-irritant and antiseptic, but is more expensive than many other equally efficacious remedies. Chloretone solution is an efficient local anæsthetic on wounded surfaces, and has been recommended in cases of gastric irritation and vomiting, which it relieves by paralyzing the terminations of the sensory nerves in the mucous membrane of the stomach.

In cases of acute **Poisoning** with chloral the treatment consists in the immediate evacuation of the stomach by the stomach tube. Emetics are of less value owing to the depression of the medullary centres. The patient ought to be kept warm and caffeine or strychnine may be given as a respiratory stimulant, while the complete failure of the breathing has to be met by artificial respiration. In acute poisoning with the other members of the series the same general treatment is to be applied, but the prognosis is much more favorable than after chloral; in one case in which 100 G. of sulphonal were swallowed, the recovery was attributed by the attendant physician to copious enemata of water. In chronic poisoning with sulphonal, the withdrawal of the drug is generally all that is required. In the chloral habit, the withdrawal has to be gradual and it may be necessary to send the patient to a retreat.

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II. STRYCHNINE—NUX VOMICA.

Strychnine is the chief alkaloid occurring in several species of Strychnos, of which the best known are Strychnos nux-vomica and Strychnos Ignatia. It is found chiefly in the seeds, and is generally accompanied by the nearly related alkaloid *Brucine*.

A large number of alkaloids have been found to resemble strychnine in their action, such as the *Thebaine* found in opium, the *Gelsemine* of Gelsemium sempervirens, and the *Calabarine* of the Calabar bean, while it is difficult to decide whether several others ought to be classed with morphine or with strychnine.

Strychnine seems to be a quinoline derivative, although its exact constitution is unknown. Its formula is $C_{21}H_{22}N_2O_2$, while that of brucine is $C_{23}H_{26}N_2O_4$. They are both derivatives of a substance of the formula $C_{15}H_{17}N_2O_2$, brucine differing from strychnine in having two methoxyl groups. It seems not unlikely that they are both nearly related to curarine, the

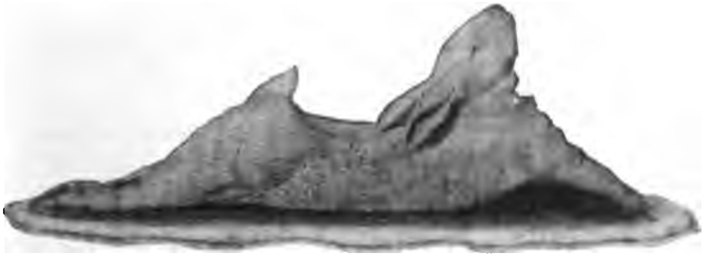
Stry. Brucine in Nux. Thebaine (opium) resembles it. CNS. esp. cord.
Bitter & improvement of appetite. Increased perception of special senses - touch
sight. hearing - first sign of stiffness of neck. then St. reflex excitability. Tremor.
Then convulsion, extensors predominating - [illegible] resp. muscles = Cyanosis
then lessened reflex [illegible] excitability + relaxation.
then another convulsion - death from asphyxia

alkaloid of curara, which is derived from some other species of the genus Strychnos.

The alkaloids of the strychnine group have a powerful stimulant action on the central nervous system, especially on the spinal cord, throughout the vertebrate kingdom.

Symptoms.—In ordinary therapeutic doses strychnine, like other bitter substances (page 54), improves the appetite and often leads to a distinct amelioration of the subjective symptoms, the patient feeling stronger and more hopeful. The pulse is generally slower and the artery feels less compressible. The special senses are rendered more acute by small quantities of strychnine, for differences can be recognized between shades of color which seem identical to the normal vision; the field of vision is widened, and in certain conditions of amblyopia light is rendered much more distinct. In the same way the hearing seems to be more acute, and the sense of touch is much more delicate. Some cases have been noted in which disagreeable odors were rendered pleasant by strychnine, but this would seem to be a rare idiosyncrasy. In cases of poisoning with strychnine, the first symptom is often a more acute perception of external objects by the senses, especially by the sense of touch, but this is not generally observed by the patient, whose first complaint is of a feeling of stiffness in the muscles of the neck and face. This is soon followed by an increased reflex reaction, so that a slight touch causes a violent movement, and even a sound or a current of air is sufficient to cause a sudden start. The increased reflex irritability is generally accompanied by some restlessness, and animals sometimes seem to make attempts to escape from bright light. Some tremor or involuntary twitches may be observed in the limbs, and then a sudden convulsion occurs in which all the muscles of the body are involved, but in which the stronger extensor muscles generally prevail. In animals the head is drawn back, the hind limbs extended, and the trunk forms an arch with its concavity backwards (opisthotonos) (Fig. 14). In man the same convulsions are seen and are accompanied by strong contraction of the face muscles, producing a hideous grin which has been called the risus sardonicus. The respiratory muscles are involved in the

FIG. 14.



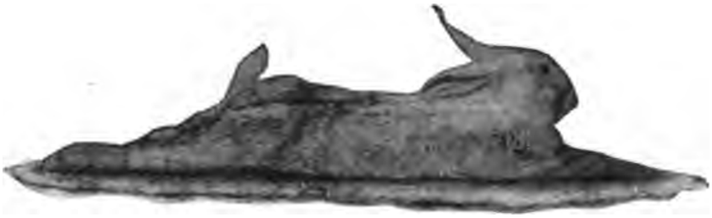
A rabbit during a strychnine convulsion.

Large quantities may paralyze cns. = death from asphyxia without convulsions

Affects cord, brain to some extent - pt conscious. Asphyxia depresses brain. Increased sense touch, taste, smell. Acts on retina, increasing vision & light sense.

general paroxysm and the blood rapidly becomes deoxygenated, as is shown by the blue cyanotic color of the lips and face in man. The muscles feel hard and firm at the commencement of the convulsion, but very soon a tremor may be made out, which becomes more distinct, and after a few intermittent contractions the animal sinks back in a condition of prostration (Fig. 15). The respiration generally returns, and becomes fairly regular for a short time. Immediately after a convulsion the reflex irritability may be low, but it soon regains its former exaggerated condition and a second convulsion occurs, exactly resembling the first. Mammals, as a general rule, succumb after two or three convulsions, the respiration failing to return after the spasm. In some cases, however, the convulsions become shorter and the intervals of quiescence longer, the respiration becomes weak, the reflex irritability gradually lessens and the animal dies from asphyxia. In frogs, where the breathing can be dispensed with for long periods, the alternation of convulsions and periods of quiescence may continue for hours or days, but these are of the same general character as those described in mammals. After very large quantities no convulsions may occur, the animal dying almost immediately of asphyxia from paralysis of the central nervous system.

FIG. 15.



A rabbit when the strychnine spasm is passing off. The head is supported to prevent its falling on the table.

Action.—The whole character of the intoxication points to an affection of the **Central Nervous System,** and it has been found that the symptoms are unaltered when the drug is prevented from reaching the peripheral nerves and muscles. The chief symptoms ~~arise from~~ the spinal cord, for the convulsions are at least as well marked in frogs and mammals in which the brain has been destroyed or severed below the medulla oblongata. At the same time the brain is also believed to be affected, though to a less degree. The intellect in man remains unclouded until the end, except for the asphyxia produced by the stoppage of the respiration; the patient is perfectly conscious of his condition, and suffers excruciating pain from the violent contractions of the muscles.

The special senses are rendered more acute by small doses of strychnine, and this is apparently due to its effects on the central nervous system in the case of touch, taste and smell, but there is reason to believe that the increase in the field of vision and the increased sensi-

Motor part of brain increased except in convulsion. Increased capacity for muscular work + less fatigue in small doses. Then depression. Convulsions are reflex from cord. Ext stimuli, even slight, necessary.

tiveness to slight differences in light are to be attributed to its acting on the cells of the retina and not to cerebral changes. For when strychnine salts are injected in the temple or applied to the conjunctiva, the sight of the corresponding eye is improved while the other remains unaffected (Filehne); if the strychnine acted centrally it could do so only by being carried to the brain by the blood, but this would affect each hemisphere equally. The affection of one eye only is explained by the strychnine diffusing through the lymph spaces, and this is said to have occurred in the case of various dyes which were applied in the same way and were then found in the retina.

As regards the effects of strychnine on the motor areas of the brain some difference of opinion exists, although the majority of those who have investigated the subject hold that the irritability of the motor parts of the cortex is distinctly increased except during a convulsion. Ergographic experiments have shown that small doses of strychnine augment the capacity for muscular work to a considerable degree, and delay the onset of fatigue. This excitation phase is followed by one in which the capacity is lowered.

The convulsions are, as has been stated, of spinal origin.[1] It has been shown in addition that they are reflex, that provided no stimulus reaches the cord from without, no convulsion occurs. As has been already remarked, the convulsions are preceded by a stage of increased reflex, and in fact the first convulsion is often seen to follow a stimulus, such as a blow or a loud noise. Afterwards they may seem to occur without any such impulse, but this is merely because a very slight or even imperceptible stimulus is enough to induce them. For example, a slight contraction of a muscle may induce a convulsion, as is seen very frequently in the frog, where a very slight stimulus, in itself apparently too weak to cause a convulsion, is followed by an ordinary reflex contraction, and this leads to a spasm. The absence of convulsions when external stimuli are cut off may, however, be demonstrated conclusively in various ways. Thus Poulsson found that a frog dipped in cocaine solution underwent no convulsions after strychnine, the cocaine used being sufficient to paralyze the sensory terminations, but not to have any direct effect on the cord. Claude Bernard showed this even more conclusively by dividing all the posterior roots of the spinal nerves in the frog and then injecting strychnine, when no convulsions occurred except when the ends of the cut roots were stimulated. The convulsions therefore follow only on the passage of an impulse from without to the spinal cord, and are merely a further development of the preceding stage of exaggerated reflex irritability. The characteristic feature of strychnine poisoning is thus the response to external stimuli. In the unpoisoned animal the reflex movement following a stimulus is always of the same kind; for example, if the leg of a decapitated frog be dipped in acid it makes certain movements to withdraw the limb, and no matter how often the

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[1] In this term is included not only the spinal cord proper, but also those parts of the brain which correspond to the cord in performing simple reflex movements.

In unpoisoned frog in acid, ant. muscles of leg contract & gastrocnem. relaxes. In strych. poisoning all inhibition removed & all muscles of leg contract, including gastroc (opp) which being stronger than ant. muscles foot is extended. Min. stim. is optimum (all or none)

irritation be repeated, the same movements are produced, though it is true that if stronger acid be used the movement is more violent and a greater number of muscles are involved. In this movement certain muscles contract while their antagonists are inhibited, for example in drawing the toe away from an irritant the anterior muscles of the leg contract, while the gastrocnemius is relaxed. The same irritation which produced in the unpoisoned animal a simple withdrawal of the limb causes after strychnine stronger and more extensive contractions, and the movement is not confined to the two hind legs but spreads over the whole body. All the muscles contract together, there being no inhibition of antagonists and the resultant movement has thus quite a different character; the gastrocnemius being stronger than the anterior leg muscles, the foot is extended and thrust against the irritant instead of being withdrawn from it. This change in the character of the reflex movement has been the subject of careful investigation by Sherrington, who finds that in mammals a stimulus which normally causes inhibition of a muscle, causes contraction under strychnine. This reversal occurs whether the stimulus is derived from the periphery and the consequent movement is a reflex one, or from the brain. In both cases the reversal of the character of the movement arises from changes in the spinal cord, the impulse from the brain or periphery bearing its normal character, but changing its nature in passing through the cord. When an external stimulus is sufficient to cause a convulsive movement in a poisoned animal, the contraction is always maximal; a stronger stimulus produces no greater effect. It must be remarked that the reflex response to different forms of stimuli is not equally altered by strychnine. The irritation of the frog's foot by very slowly acting substances, such as dilute acids, may be followed by an ordinary reflex movement, while a sudden shock causes a violent convulsion.

FIG. 16.

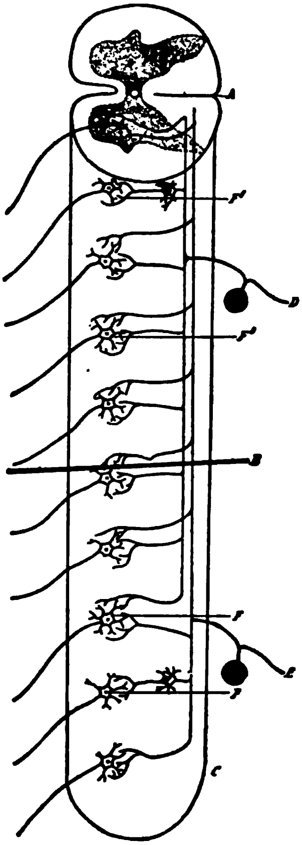


Diagram of the spinal cord of the frog. *A–B*, the part of the cord exposed to strychnine. *B–C*, the unaffected zone. An impulse reaching the cord through the sensory fibre *E* passes to the motor cells *FF* and induces an ordinary reflex movement, showing that the cells *FF* are not altered by strychnine. On the other hand, an impulse reaching the cord through the sensory fibre *D* causes tetanic convulsions not only in the muscles supplied by the motor cells *F' F'*, which are under the influence of the poison, but also in those supplied by *FF*, which have been shown to be free from the strychnine action.

Inhibition destroyed therefore impulse strikes different cells with great force = much reaction + loss of coordination.
Not complete removal of inhibition, as impulse along usual path the stronger

There are strong grounds for the belief that the cells of the anterior horn are not necessarily involved in the strychnine action (Fig. 16). For when strychnine is applied in solution to the cord of the frog at the level of the cells connected with the nerves to the fore limbs, irritation of the foot produces an ordinary response in the hind limbs, while the anterior port of the body remains motionless; that is, strychnine has not penetrated to the cells connected with the hind limbs. Irritation of the fore limbs, on the other hand, produces tetanus not only of these, but also of the hind limbs, although the motor cells of the hind limbs have been shown to be outside the poisoned area. Tetanus can, therefore, be produced in parts whose motor cells are unpoisoned. The increased strength of the contraction is due, not to augmented energy in the anterior horn cell, but to the impulses which these receive being much stronger. This experiment suggests further that the synapse round the motor cell is not the point chiefly affected by strychnine. And the posterior root ganglion is not the seat of action, for convulsions may be elicited by stimulation of the posterior roots above this point. The action may thus be localized in some point between the entrance of the afferent fibre and the synapse round the motor cell. The depressants of the alcohol-chloroform group appear to act at the same point as strychnine (p. 163).

An impulse travelling up a nerve in an unpoisoned frog reaches the cord and may there pass through a number of paths and in each is subjected to various influences, so that it arouses different motor cells to different degrees of activity, or actually inhibits the activity of some of them; in this way a coördinated movement follows. Under strychnine these influences, which may be figured as varying resistances in the different paths, disappear, and the impulse passes untrammeled along all available paths and reaches the motor cells in much greater force than normally and thus arouses a more powerful reaction from them and a correspondingly strong muscular contraction. But the resistance in the different paths is essential to coördinate the movement and the increased muscular contraction is thus no longer coördinated, all the muscles contracting together and the character of the movement being determined by their relative strength. The action of strychnine may thus be explained by supposing that it removes resistances to the passage of impulses through some of the synapses of the spinal cord and thus extends the area on which an impulse acts, and also liberates it from the normal coördinating influences.

It must be remarked that while the resistance is much reduced, it is not entirely removed and the ordinary path is still somewhat more easily traversed than the others, for very weak irritation often causes an ordinary reflex response in the frog, while a slightly stronger stimulus throws it into opisthotonos. Baglioni has recently shown that a single stimulus is not sufficient to cause complete tetanus, but that the movement induced by the first shock leads to secondary stimuli arising from the joints and tendons which are moved; the arrival of these secondary stimuli in the cord maintains it in activity, [illegible] = contraction which acts as stim till cord exausted then relaxation till recovers irritability. Tone of medulla & its reflexes increased by small doses. Eventually cord paralysis. No direct action on muscle. Nerve ends may be paralyzed. Resp up. then ceases. None during spasm of diaphragm

Heart not directly unless small dose = tone of c. inhib = decreased rate. large dose depresses small dose increases rate

and the muscles consequently remain contracted until the cord is fatigued and refuses to react to the persistent stimuli from the periphery. The muscles then relax and an interval of quiescence follows until the cord has recovered its irritability.

Besides the spinal cord, all other regions in which simple reflex can be produced, are affected by strychnine. Thus the medullary centres are thrown into the same condition, and their responses to stimuli are equally exaggerated; but they are in constant receipt of impulses, and strychnine by increasing the efficiency of these augments the tone of the medulla oblongata, when it is given in small quantities.

Artificial respiration has been shown to delay the onset of convulsions in animals, but it is still an open question whether this is due to the better aëration of the blood (Osterwald) or to the effects of the mechanical movements (Gies and Meltzer).

The stimulation of the spinal cord by strychnine is followed by depression and paralysis. Even during the first stage the stimulation is mixed with depression, for though a more violent response is induced by a sensory stimulus, this cannot be repeated so often as in the normal frog, as the cord becomes fatigued more readily. The sensory part of the spinal cord seems to be paralyzed somewhat earlier than the motor cells, but these also lose their irritability after a time and no further movement can be elicited either by reflex or by direct stimulation of the cord.

Strychnine seems to have no direct action on the voluntary **Muscles**; it is stated that minute quantities increase their tone, that is, render them more tense, so that they are prepared for immediate contraction, but this is due to action on the cord and not on the muscle fibres.

The **Terminations of the Motor Nerves** are paralyzed by large doses of strychnine in the same way as by curara. This effect is scarcely seen in mammals, as central paralysis always precedes it and destroys life, but in some species of frogs the nerve ends are paralyzed before the central nervous system. This paralysis is not due to the exhaustion of the nerve ends through the tetanus, but is a direct action on the terminations, although the exhaustion may contribute to the result.

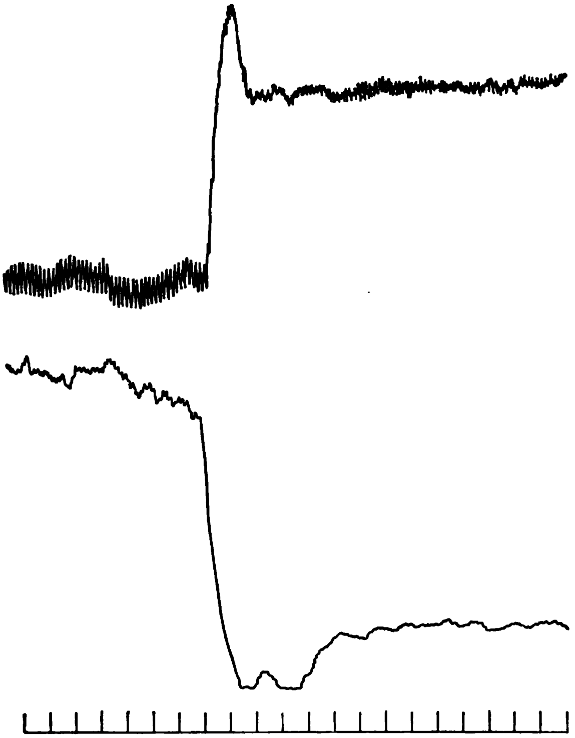
The **Respiration** is quickened and deepened by small quantities of strychnine, especially when the centre is depressed by the previous administration of a narcotic. During the convulsions the breathing is arrested by the violent contraction of the diaphragm and the other respiratory muscles, but during the intermissions it continues fairly regular. After one or two spasms it often fails to be reinstated, and the animal dies of asphyxia; in other experiments it undergoes a gradual diminution in rate and strength, and eventually ceases from gradual paralysis of the centre.

The **Heart** is not directly affected by strychnine in mammals, though it is sometimes slightly slowed by stimulation of the inhibitory centre. During and after a convulsion it may be accelerated as in violent exertion from any cause. Very large quantities slow and weaken the frog's heart.

Ves. const. of splanchnics esp. in convulsion + b.p. up. Relaxation = lessened activity of center & effete muscle products lowers it.

The **Vasomotor Centres** are stimulated by small quantities, so that the splanchnic vessels are constricted, while the cutaneous and perhaps the muscular vessels tend to dilate from stimulation of the vasodilator centre. The blood is thus deflected to some extent from the internal organs to the skin and limbs. Larger quantities tend to disorganize the vasomotor centre in a way analogous to that described in the spinal cord, for Bayliss finds that inhibitory reflexes involving the vasomotor centre are changed to motor ones; thus stimulation of the depressor nerve after strychnine causes a rise in blood-pressure.

FIG. 17.



Blood pressure (upper) and intestinal volume (lower) tracings from a curarized cat, showing the effect of the intravenous injection of a dose of strychnine sufficient to cause spasms in an uncurarized animal. The blood pressure rises, while the mesenteric vessels are contracted from spasm of the vasomotor centre (Bayliss).

During the convulsions the blood-pressure is raised to an extreme height, partly owing to the activity of the vasomotor centre and perhaps partly from the blood being pressed out of the abdominal organs and the muscles by the violent contractions. Immediately after a convulsion the blood-pressure falls, probably from the exhaustion of the centre. The blood-pressure remains elevated much longer in curarized than in uncurarized animals, which would seem to indicate that the fall in pressure is partly due to the substances produced by muscular activity.

Bitter. Auerbach's ~~[illegible]~~ = bitter [illegible]. Generally increased
metabolism. More heat produced but skin dil. Out urine for 3-8 days
Very slight tolerance. Brucine much the same but 35 X weaker

In the **Alimentary Tract,** strychnine has the same action as any other bitter substance, and it produces a flow of saliva and increased appetite if taken before meals. (See Stomachic Bitters, page 54.) It seems to be absorbed from the intestine mainly. After absorption it probably increases the movements of the bowel, apparently from some action on the muscle or on the ganglionic plexus in the bowel wall.

Metabolism.—Strychnine produces an enormous activity of the muscles, and, therefore, increases very greatly the consumption of oxygen and the output of carbonic acid. This increased excretion of carbonic acid occurs, though to a less extent, even when the muscular contraction has been previously eliminated by curara, and must, therefore, be due in part to the contraction of the involuntary muscle of the vascular walls and perhaps to the increased metabolism of the central nervous system.

The augmentation of the oxidation in the tissues is accompanied by an increased formation of heat, which would lead to a rise in the temperature of the body were it not counteracted by an equal or even greater increase in its dissipation through the skin. The result of the interaction of these two factors is that in spite of an increased warmth production the internal temperature is generally lowered in rabbits, while a slight rise in the thermometer is sometimes seen in dogs and cats. The skin temperature, on the other hand, rises considerably because more blood flows through it than usual.

In the frog, the administration of strychnine is often followed by glycosuria. This does not seem to occur in adult mammals, but is sometimes observed in young dogs, in which, as in frogs at certain seasons, there is a large accumulation of glycogen in the liver. Demant states that strychnine, even in small quantities, causes the glycogen of the liver and muscles to disappear; the increased muscular movement and the disturbance of the respiration are probably the explanation of both of these phenomena.

Strychnine is eliminated in the urine chiefly. Its excretion begins three hours after its injection, but is exceedingly slow, and the reaction is often given by the urine for three to eight days afterwards. Traces of the alkaloid also appear in the stomach after its hypodermic injection, and it is not improbable that some of it undergoes oxidation in the tissues.

Only a very slight degree of tolerance is developed for strychnine, even after very prolonged administration.

The action of strychnine is almost identical throughout the vertebrate kingdom. Man is more susceptible than other mammals, and young animals are more refractory than adults, perhaps owing to the less developed condition of the central nervous system. The domestic fowl tolerates comparatively large quantities without symptoms. The characteristic convulsant action is not elicited in most invertebrates, in which it generally induces paralysis only.

Brucine, the second alkaloid of nux vomica, resembles strychnine closely in action but is much weaker, from 30 to 40 times as large a dose being required to produce the same effect. It differs from strychnine also in possessing a much more powerful action on the nerve terminations in volun-

Nux .9–2% strych .7–1.5% brucine Pd. 1–4 gr
As bitter (~~tinct~~) = appetite, nutrition, general "betterment of tone". CNS.
reflexes increased ~~and~~ a true "tonic"
CNS. in paralysis without CNS lesion or without irritation. In Pb poison parag
Caffeine. ~~Atropine~~ & Camphor are the other CNS. stim

tary muscle, especially in some species of frog. It is credited with weak local anæsthetic properties.

Calabarine and gelsemine are chiefly of interest as impurities which occur along with the more important alkaloids of the Calabar bean and of Gelsemium, while thebaine forms a connecting link between the opium alkaloids and strychnine, and will be discussed along with the morphine series; it seems to stand midway between strychnine and brucine in toxicity.

PREPARATIONS.

Nux Vomica (U. S. P., B. P.), the seeds of Strychnos nux-vomica, contains 0.9–2 per cent. of strychnine and 0.7–1.5 per cent. of brucine, along with tannin, which gives a dark green coloration with iron salts. The powdered bean is occasionally prescribed in doses of 0.06–0.25 G. (1–4 grs.).

✓ EXTRACTUM NUCIS VOMICÆ (U. S. P., B. P.), 0.015–0.06 G. (¼–1 gr.).

Fluidextractum Nucis Vomicæ (U. S. P.), 0.05 c.c. (1 min.).

✓ *Extractum Nucis Vomicæ Liquidum* (B. P.), 1–3 mins.

✓ TINCTURA NUCIS VOMICÆ (U. S. P., B. P.), 0.3–1 c.c. (5–15 mins.).

Strychnina (U. S. P., B. P.), 0.001–0.002 G. ($\frac{1}{60}$–$\frac{1}{30}$ gr.).

STRYCHNINÆ NITRAS (U. S. P.), 0.001–0.002 G. ($\frac{1}{60}$–$\frac{1}{30}$ gr.).

STRYCHNINÆ SULPHAS (U. S. P.), 0.001–0.002 G. ($\frac{1}{60}$–$\frac{1}{30}$ gr.). $\frac{1}{60}$–$\frac{1}{30}$ gr

STRYCHNINÆ HYDROCHLORIDUM (B. P.), $\frac{1}{60}$–$\frac{1}{15}$ gr.

Liquor Strychninæ Hydrochloridi (B. P.) (1 per cent.), 2–8 mins.

Ferri et Strychninæ Citras (U. S. P.), 0.06–0.2 G. (1–3 grs.).

Glyceritum Ferri, Quininæ et Strychninæ Phosphatum (U. S. P.), 1 c.c. (15 mins.).

Syrupus Ferri, Quininæ, et Strychninæ Phosphatum (U. S. P.), 4–8 c.c. (1–2 fl. drs.).

Syrupus Ferri Phosphatis cum Quinina et Strychnina (B. P.), ½–1 fl. dr.

The extract is generally prescribed in pill form, while strychnine sulphate or hydrochlorate may be given in solution, pill or tablet; where rapid action is desired, it is injected subcutaneously. The tincture is largely used as a stomachic bitter, and the iron preparations in conditions of general debility. The preparations of the U. S. P. are standardized, the extract containing 5 per cent., the fluidextract 1 per cent. and the tincture 0.1 per cent. of strychnine.

Therapeutic Uses.—Strychnine is used largely for its local action on the digestive organs as a stomachic bitter, and is generally prescribed in the form of the tincture or one of the extracts for this purpose, as in this way it is much less liable to absorption than when given as an alkaloidal salt. It may be combined with the cinchona preparations or with one of the simple bitters.

Small quantities of strychnine are of benefit in many ill-defined conditions of weakness, cachexia and "want of tone" generally. The results are probably partly due to its stomachic effects in increasing appetite and digestion, but the action on the central nervous system cannot be overlooked. The slight increase in the irritability of the cord probably leads to an improvement in almost all of the nutritive functions through increasing the contraction of the vessels and producing greater activity of the muscles. In this way strychnine perhaps deserves the name of "tonic" more than most of the drugs to which it is applied.

As a stimulant to the central nervous system[1] strychnine has found

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[1] Other central nervous stimulants are **Caffeine, Atropine, Camphor.**

Stim resp. + cough in moderate doses. Large doses paralyzes center (Shock, Anaesthesia) Caffeine, atropine also good. Some eye cond. improved. Of little value in hrt cond.— esp shock &c. May constrict vessels(?). Center depressed. Used to counteract depression of alcoholism

wide application in almost every form of paralysis, and as long as distinct anatomical lesions of the central nervous axis are absent, it may be of benefit; for instance, it is often valuable in lead poisoning; but where the continuity of the axis is broken by hæmorrhage or by the destruction of the nerve cells, little improvement is to be anticipated from its use, though it may serve to delay or prevent the atrophy of peripheral nerves and muscles in some of these cases. When the paralysis is due to an inflammatory process, strychnine is to be used with the greatest care, or is perhaps better avoided entirely as long as the irritation is present, as it seems to increase and prolong the inflammation when used early in these cases.

Strychnine is used as a respiratory stimulant in some forms of pulmonary disease in which it is desirable to increase the respiration or to provoke coughing. It has been advised in failure of the respiration during anæsthesia, and is certainly more likely to be beneficial than the great majority of drugs suggested for this purpose. Too large doses must not be injected in these cases, however, as strychnine paralyzes the respiratory centre itself when given in excess. In other forms of poisoning in which the respiratory centre seems in danger, and in shock, strychnine may also be of service, especially when it is injected hypodermically. Other respiratory stimulants which may be substituted for strychnine for some purposes are caffeine and atropine.

In amaurosis or amblyopia unassociated with atrophy of the optic nerve, and even in commencing atrophy, strychnine has frequently improved the vision. In many cases it fails to produce any benefit, and the exact conditions in which improvement can be looked for are unknown.

Strychnine seems to be of benefit in some cases of heart disease and is often supposed to have a direct action on that organ. Any improvement which may be produced by it, however, must be attributed to the constriction of the vessels, and the indications for its use would seem to be a low blood-pressure. Crile denies it any value in the treatment of the low blood-pressure of shock, however, and Cabot could not find any change in the blood-pressure after its use in a number of conditions in which it is ordinarily advised. There seems no question that its value in heart disease is often overestimated, and that little dependence can be placed on its benefiting these cases.

Strychnine is said to be of value in chronic alcoholism in lessening the depression which forms one of the chief difficulties in the treatment.

The other alkaloids of this series do not seem to have any properties which would entitle them to a position in therapeutics.

Poisoning.—In cases of strychnine poisoning, the first treatment consists in the evacuation of the stomach by means of emetics, or, better, by the stomach tube; it may be necessary to give chloroform as the attempt to pass the tube is often followed by violent convulsions. Preparations of tannic acid, such as strong tea, may be given in order to form the insoluble tannate, which, however, must be removed as quickly as possible, as it is broken up by the acid gastric juice and

Poisoning – Stomach tube (maybe under chlor). Tr. then remove to prevent gastric juice [illegible] & stry rapidly absorbed. Chlor (a little) allays convulsions. Chloral can't be removed if paralysis comes on. Then artificial resp – but prognosis poor as excretion so slow.

the strychnine is rapidly absorbed. To combat the convulsions, depressants to the central nervous system should be given, and, although chloral is usually advised, chloroform or ether is often preferable. It is unnecessary to produce deep anæsthesia, a few whiffs of chloroform being often sufficient to allay the convulsions. The advantage of the anæsthetics over chloral is that they can be removed if any symptoms of strychnine paralysis appear. Opium has been suggested, but is not nearly so efficacious in strychnine poisoning as members of the methane series. If the paralysis comes on, artificial respiration may be attempted, although the poison is excreted too slowly from the organism to permit of much hope of recovery.

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In addition, strychnine was studied by Magendie, Cl. Bernard and Orfila and their works ought to be consulted for the earlier history of the poison.

III. PICROTOXIN.

Picrotoxin is the best known member of a group of convulsive poisons, which resemble each other very closely in action, but of whose chemistry little is known beyond the fact that they are devoid of nitrogen. It is obtained from the Anamirta paniculata (Anamirta cocculus, Menispermum cocculus), and is a neutral indifferent body. Picrotoxin ($C_{30}H_{34}O_{13}$) may be broken up into picrotoxinin ($C_{15}H_{16}O_6$), which resembles it in its effects on animals, and picrotin ($C_{15}H_{18}O_7$), which is inactive.

Other poisons resembling picrotoxin are *Cicutoxin,* derived from the Cicuta virosa, or water hemlock, and probably from other species of Cicuta, *Œnanthotoxin,* the active principle of Œnanthe crocata, water dropwort, or dead tongue, and *Coriamyrtin,* which occurs in several species of Coriaria, of which the best known is the Coriaria myrtifolia or currier's sumach. Another species of Coriaria affords the toot poison of New Zealand. *Phytolaccotoxin,* which has been prepared from a Japanese species of Phytolacca, resembles picrotoxin in its action and may probably be contained in the official (U. S. P.) Phytolacca decandra, or pokeberry. Lastly, a number of the members of the digitalis series may be decomposed into bodies which, devoid of the

Clonic convulsions · seizen = prolonged spasms

characteristic cardiac action of digitalis, produce the same symptoms as picrotoxin. Among these may be mentioned *Toxiresin*, obtained from digitoxin, *Digitaliresin* from digitalin, and *Oleandresin* from oleandrin. These bodies all produce powerful stimulation of the central nervous system, more especially of the areas around the medulla oblongata. The chemical connection between them and the members of the digitalis series has been mentioned already. It may be added that the two groups are similar in action in some respects, for although picrotoxin does not affect the heart and vessels in the same way as digitalis, the latter possesses the characteristic action of picrotoxin on the medulla oblongata, although in a weaker degree; in fact, some of the remedies described under the digitalis series act as strongly on the central nervous system as on the heart. Picrotoxin resembles camphor also in its effects. Two alkaloids, *Samandarine* and *Samandaridine,* recently isolated by Faust from the skin of the newt appear to resemble picrotoxin in their effects on animals.

Symptoms.—The symptoms, which are often somewhat late in appearing, are very similar in all classes of vertebrates. In man vomiting is not infrequently observed after members of this series, or the first symptoms may be salivation, acceleration of the respiration, and some slowness of the pulse and palpitation of the heart. A condition of stupor and unconsciousness follows and then a series of powerful convulsions, which, commencing in tonic spasms, soon change to clonic movements of the limbs and jaws. The respiration is interrupted during these spasms, but is reinstated during the intervals of quiet and collapse which follow them. The convulsions return after a short pause, and this alteration of spasm and quiet may continue for some time, although the respiration often fails to return after one of the spasms, and fatal asphyxia results.

Similar effects are observed in the lower mammals. After a preliminary stage in which twitching of the muscles and vomiting often occur, and in which the respiration is accelerated, while the pulse is slow, a violent emprosthotonic convulsion sets in, but soon changes to clonic movements; these may last for some time, but eventually become weaker and give place to a condition of quiet and depression. An increase in the reflex excitability is noticeable during this interval, the animal is easily startled and occasional twitching of the muscles may be observed. Very soon a second convulsion sets in, and this may be fatal from asphyxia, but the symptoms often continue for an hour or more, violent spasms alternating with periods of depression and collapse. In the frog clonic convulsions are also the chief feature of the intoxication. Very often the animal becomes distended with air during the convulsions, and gives a curious cry in releasing it. The heart is always slowed and may cease to beat altogether for a time.

Action.—The clonic convulsions of picrotoxin poisoning are altogether different from those of strychnine and other similar bodies, which induce prolonged tonic convulsions, and it was early surmised that the members of this series act on a different part of the **Central Nervous System.** The convulsions are found to persist in the frog after the cerebrum has been destroyed, and even when all of the brain above the

Action on medulla — resp up. heart down. vomit & salivation, + V.C. cns active so b.p. way up. Frog — spasm —] laryngeal muscles — so bloated little peripheral action. In very small doses, it lowers temp as other convulsive poisons

medulla oblongata has been removed, although they are weakened by the destruction of the optic lobes. On the other hand, they disappear, or at any rate lose their typical character when the medulla oblongata is removed, so that it would seem that picrotoxin and its allies act chiefly on the medulla oblongata, while the spinal cord and the higher parts of the brain are comparatively little affected. Strychnine, on the other hand, exercises its chief action on the spinal cord, while the other parts of the central nervous axis are less affected. It is not unlikely that in animals higher in the scale than the amphibia the action of picrotoxin extends to the pons and possibly to some of the cerebral nuclei, but this has not been ascertained with certainty, though it is suggested by the analogy with camphor and also by the fact that picrotoxin often induces restlessness and increased movements before the onset of convulsions. The effects of the stimulation of the centres in the medulla are seen in the acceleration of the respiration, in the slow pulse, which is due to inhibitory action, in a very marked rise of the blood-pressure, and in the vomiting and salivation. In many animals the reflexes are found to be increased when the medulla is severed from the cord, and this indicates that the spinal cord is also more excitable than normally. This action on the spinal cord is best seen in the fish and reptile, and is much less marked in the frog and mammals. In the former, picrotoxin causes convulsions even after the medulla oblongata is removed, but in the higher animals, in which the functions are more differentiated, it merely increases the reflexes or causes very slight convulsive movements.

The **Heart** is rendered slow by picrotoxin, and in the frog may come to a standstill during the convulsions. This is due principally to stimulation of the inhibitory centre in the medulla, since on division of the vagi the heart returns to almost its normal rate. Some direct depression of the heart is observed after large doses, for the pulse remains slowed even after atropine or division of the vagi. Picrotoxin causes a very marked rise in the arterial tension from stimulation of the vaso-constrictor centres in the medulla and upper part of the cord.

The **Respiration** is accelerated before any convulsions set in, and in the intervals between the spasms is also very rapid, owing to the action on the centre. Late in the intoxication the breathing may become slow and labored, probably from approaching central paralysis. In the frog, spasm of the laryngeal muscles prevents the escape of air from the lungs, so that the animal becomes enormously inflated.

The **Vomiting** often observed in man and the dog under picrotoxin is probably of central origin and not due to gastric irritation.

The peripheral **Nerves** and **Muscles** do not seem to be affected by these poisons, with the exceptions of toxiresin and digitaliresin, which slightly lessen the irritability of the muscles.

The fate of picrotoxin in the body and the way in which it is excreted are unknown. Like other convulsive poisons, it tends to lower the temperature when it is given in quantities insufficient to cause convulsions.

Chloroform or chloral etc stop convulsions. Us[ed] in skin diseases or as emetic. Possibly to counteract effects of narcotics – raises b.p., resp + heart & brings to consciousness (Coriamyrtin better). By increasing resp may remove effete matters which ~~cause~~ excite perspiration center at night in phthisis

The convulsions of picrotoxin and its allies disappear when chloroform or chloral is administered. On the other hand, the respiration, weakened by narcotic poisons such as chloral, is accelerated by picrotoxin, the blood-pressure rises, and the sleep is less prolonged. Animals are not awakened at once from narcosis by picrotoxin, but coriamyrtin has this effect.

Picrotoxin is not antidotal in morphine poisoning in animals, but may possibly be so in man (see page 224).

PREPARATIONS.

Picrotoxinum (B. P.), picrotoxin ($C_{30}H_{34}O_{13}$), a neutral principle obtained from Anamirta paniculata, slightly soluble in water, much more so in alcohol. 0.001–0.003 G. ($\frac{1}{60}$–$\frac{1}{20}$ gr.).

Phytolacca (U. S. P.), the root of Phytolacca decandra, or pokeroot.

Fluidextractum Phytolaccæ (U. S. P.), 0.3–2 G.

Therapeutic Uses.—Picrotoxin has been used as an ointment to destroy pediculi, and in some forms of skin disease, but is too poisonous to be recommended for this purpose. It has been proposed to give it by subcutaneous injection in cases of collapse and in narcotic poisoning, but according to Köppen, coriamyrtin is more efficient in animals. It has not been employed for this purpose in therapeutics as yet. It has some reputation in the profuse night-sweats of phthisis, which it diminishes in a certain proportion of cases, probably by increasing the respiration and thus preventing the stimulation of the nervous mechanism of perspiration through the partial asphyxia. Phytolacca has been advised as an emetic, but is slow in action and dangerous. It is seldom prescribed, and appears to be superfluous, at any rate until its action has been ascertained with more certainty.

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IV. OPIUM SERIES.

Opium has been used in medicine since a very remote period, and although many substitutes have been proposed for it of late years, it still occupies a position of its own in therapeutics. It is the dried juice of the Papaver somniferum, a poppy which is grown chiefly in India, China, Egypt, Persia and Asia Minor, but has been cultivated in colder climates and is said to produce a more powerful opium there. Opium owes its activity to a large number of alkaloids, of which *Morphine* is the most important. Others are *Codeine, Pseudo-*

Average % of morphine in opium is 10%, codeine .5%. thebaine .3% etc
Eff. dep. on diff animals. Frogs relatively insusceptible.

morphine, Thebaine, Codamine, Laudanine, Laudanosine, Papaverine, Meconidine, Lanthopine, Cryptopine, Protopine, Papaveramine, Rhœadine, Narcotine, Oxynarcotine, Narceine, Hydrocotarnine, Gnoscopine and *Tritopine.* Many of these, however, occur only in traces. The total amount of alkaloids in opium varies from about 5–25 per cent., and different specimens may contain very different quantities of each alkaloid; for instance, morphine may vary from 2.7–22.8 per cent. The average percentage of morphine is 10, of narcotine 6, papaverine 1, codeine 0.5, thebaine 0.3 and narceine 0.2; the others occur in too small quantity to have any influence on the action of the crude drug. The alkaloids are found in opium in combination with meconic, lactic and sulphuric acids. The empirical formulæ of most of the alkaloids have been determined, those of the most important being morphine ($C_{17}H_{19}NO_3$), codeine ($C_{18}H_{21}NO_3$), narcotine ($C_{22}H_{23}NO_7$), papaverine ($C_{20}H_{21}NO_4$), thebaine ($C_{19}H_{21}NO_3$). Morphine, codeine and thebaine are derivatives of phenanthrene ($C_{14}H_{10}$), a hydrocarbon isomeric with anthracene; in morphine this contains two hydroxyls and is combined with a nitrogenous radicle known as morpholine.[1] In codeine one of the hydroxyls is substituted by methoxyl, and in thebaine both are thus substituted and some other changes occur in the constitution. Narcotine, papaverine and some of the other alkaloids are isoquinoline derivatives.

The action of opium is mainly due to the large amount of morphine contained in it, though the other alkaloids may reinforce its effects. Morphine acts chiefly on the central nervous system, but it also affects some peripheral organs, such as the intestine. Its action varies considerably in different animals, and it is therefore necessary to consider its effects at some length upon the different classes.

Symptoms.—The **Frog** is remarkably tolerant of morphine, no change whatsoever following the injection of quantities which would cause distinct symptoms in man. The first symptoms elicited are a diminution of the spontaneous movements; the animals sits still unless disturbed, but then moves in a perfectly normal manner. Later the movements become clumsy and ill-coördinated, and at the same time they are elicited less easily. At a somewhat more advanced stage of the intoxication the animal makes no movement when placed in abnormal positions, as on its back, which indicates that it has lost entirely its power of preserving its equilibrium. The spinal cord maintains its irritability, but in a lower degree than usual, as is shown by the reflex movements being weaker than in the unpoisoned frog. This condition may last for several hours, when a series of symptoms of an entirely different nature appear. The reflex response to irritation is distinctly depressed during the first stage, but in this second phase it begins to return, and eventually a condition of exaggerated

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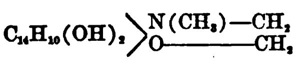
[1] The formula for morphine accepted as most probable at present is



$$C_{14}H_{10}(OH)_2\begin{matrix}\diagdown N(CH_3)-CH_2\\ \diagup O\text{———}CH_2\end{matrix}$$

Mammals: depression of voluntary movements [illegible] [illegible] excitability. Cats are excited - lead to convulsions. Dog = sleep but easily aroused. Diminished pain, asphyxia. For other signs see below.

reflex irritability sets in. This development first affects the muscles of respiration, but soon spreads over the whole spinal cord, so that the condition comes to resemble exactly that noted in strychnine poisoning, except that the frog seems more easily exhausted than after moderate quantities of strychnine. The same tetanic contractions of the muscles are to be seen, however, with opisthotonos and cessation of the respiration, interrupted by periods of quiescence and exhaustion. The animal may recover from this stage, in which case it again passes through the stage of depression, but it frequently dies during it from exhaustion and paralysis of the central nervous system.

In **Mammals** morphine produces symptoms resembling those seen in the frog, first depression of the voluntary movements, and later a marked increase in the reflex irritability. The relative importance of these two stages differs, however, in the different classes, and indeed in different individuals of the same class. Thus in the cat and in all the other felidæ, and in the horse and ass, morphine seems rather to increase than to diminish movement. The animal runs about the room or in a circle and seems unable to remain at rest for a moment. At the same time a depression of the intelligence and of the power of perception makes itself manifest, for no definite attempts at escape are made and obstacles are not avoided so carefully as by the unpoisoned animal. Eventually convulsions similar to those seen after strychnine are developed. In the dog, on the other hand, the depressant action of the drug is the more highly developed, at any rate after small doses. The first symptom is not infrequently vomiting and defæcation, and then the animal passes into a light sleep, from which he can be easily aroused by touching or by noise, but which rapidly becomes deeper, so that greater force has to be used to waken him. When once awakened, he seems to sleep less heavily for a short time, and a much slighter stimulus is enough to arouse him if it is applied soon afterwards. When awakened he may perform apparently voluntary movements for a short time, although more clumsily than in his normal state, but no complete consciousness is present, the animal is stupid and drowsy and soon sinks back into deep slumber again. The sensation of pain seems to be much lessened but not entirely abolished, and reflex movements are difficult to elicit. After larger quantities an exaggerated sensibility to external stimulation seems present, for the animal starts convulsively at loud sounds and on pinching, but when left undisturbed lies in profound sleep. The respiration is at first quick and dyspnœic, the dog panting as if after a long run, but later it becomes slow and labored; the pupil is narrowed; the circulation seems less affected, although a congestion of the skin and mouth is often observed. The stage of strychnine-like convulsions is not developed in the dog, although the reflex irritability may be distinctly increased by large quantities. Just before the respiration finally ceases, convulsions generally occur, but these are asphyxial in origin and are not due to the direct action of the alkaloid. In the rabbit and other rodents the symptoms are similar to those seen

Man – 1/8 gr. lessens vol. movements – drowsiness – sleep. Can be kept awake by continued stim. but no attention. No increase in intellect. power but images vivid = dream. imagination. No conception of time

1/4–1/2 gr. = deep dreamless sleep – easily aroused, returns easily. May lead to torpor & coma when continuous. Pulse full. resp. slow. Pupils pin point. Cheyne Stokes even. Cyanosis then small quick pulse. Asphyxia & widening of pupils

in the dog, but the depression is even more marked. An increase in the reflex irritability to external stimulation is also evident here, while the respiration is slowed from the beginning. Small quantities of morphine produce drowsiness in the horse, ass or goat, larger quantities restlessness and excitement which may pass into convulsions and death.

In **Birds** morphine causes vomiting, drowsiness, sleep and stupor, with slow and imperfect respiration, very much as in mammals; in common with all the lower animals they are much less susceptible to its influence than man, but the tolerance does not seem greater than that of rabbits and dogs when the drug is administered hypodermically. It seems to be absorbed with difficulty from the crop.

In **Man** small quantities of morphine (⅛ gr.) lessen the voluntary movements and produce a drowsiness which soon passes into sleep, unless the patient is continually aroused by his surroundings. As long as he is kept awake, his actions and movements show nothing abnormal, but it is impossible to keep his attention directed to any object for long, and as soon as he is left to himself for a few moments he sinks into sleep. After small quantities there is no difficulty in arousing him; in fact, the sleep seems lighter than usual and may resemble rather a state of abstraction or "brown study." In this condition the imagination is not depressed to the same extent as the reason, and it is often stated, therefore, that opium at first stimulates the intellectual powers. This is incorrect, however—the self-control and judgment are lessened, and although the stream of thought may seem more rapid and the images more vivid than usual, the logical sequence is lost, and the condition may rather be compared to dreaming than to a real increase of the intellectual powers. In particular, the patient has often no idea of time. This stage of abstraction is not by any means generally observed and soon passes into sleep, but the unchecked imagination may still persist in the form of dreams.

In larger quantities (¼–½ gr.) morphine produces deep, dreamless sleep, from which the patient is still easily aroused, but which returns at once when he is left undisturbed. When once aroused, he can be kept awake or can be aroused again after a short interval much more easily, some time elapsing apparently before the same degree of depression is reached again. As the dose is increased, the sleep deepens into torpor, from which he can be wakened only with difficulty, and eventually all efforts to arouse his attention are fruitless and he sinks into coma, which may be reached very soon after a large dose. During this deeper sleep and coma the respiration is very slow, the pulse is regular, full and of moderate speed. The pupils are contracted to a small point and the mouth and throat are dry. The face is purple and congested, and the skin feels warm, although the temperature may be low. The breathing generally becomes slower and weaker, and occasionally periodic (Cheyne-Stokes). The cyanosis increases, the pulse becomes smaller and often quicker, the pupils remain contracted, but dilate widely just before the final arrest of the respiration. The heart continues to beat feebly for a short time afterwards.

Small doses awakens refreshed but dry throat, nausea. Rarely delirium. Depression of higher brain. Stim of cord (in later period or large doses). Motor function depressed. Cord mind depressed by chloral

After small doses of morphine the patient generally awakes refreshed, and, save for an occasional dryness of the throat and slight nausea, apparently quite normal. Not infrequently, however, headache is complained of, and sometimes nausea and vomiting, accompanied by marked depression. In rare cases delirium, and even convulsions, have been observed soon after its injection, but these symptoms of excitement are so rare in the human subject as to be classed as idiosyncrasies. Some skin affections, such as itching and redness, are occasionally seen while the action is passing off.

Action.—The action of morphine on the **Central Nervous System** seems to consist then of a mixture of stimulation and depression, which are not equally marked, however, throughout the divisions of the central axis. The depression seems to be produced mainly in the brain, especially in those parts associated with the higher intellectual faculties, while the stimulation affects first the spinal cord. It seems likely that in different animals these two opposing influences prevail to varying extents, so that in some the stimulant action extends to the brain, as in the cat, while in man the depressant action dominates the whole central nervous system, at any rate when moderate quantities are used. The action on the brain is elicited by smaller quantities than that on the cord, so that the first effect of morphine is general intellectual depression, while the increased activity of the spinal functions is only elicited by very large quantities. This selective action of morphine is especially evident in the medulla oblongata, in which certain centres are entirely paralyzed before neighboring ones undergo any distinct modification.

Morphine, therefore, seems to combine in itself the properties of alcohol and of strychnine; like the former, it depresses the functions of attention and coördination of the brain, while, like the latter, it increases the activity of the spinal cord.

The effect of morphine on the **Spinal Cord** has been studied almost exclusively in the frog. The reflex irritability in these animals is first diminished to a slight extent, and then increased to the same degree as by strychnine. It seems difficult to believe that the same drug should cause first depression and then stimulation of a function, but it has been shown in the description of the action of strychnine that all the elements of the spinal cord are not involved in the changes produced by that poison, and a possible explanation would be that while small quantities of morphine lessen the ability of the motor cells to give out impulses, larger quantities increase the activity of the receptive and transmitting cells, so as to compensate for the depression of the motor cells and eventually to conceal their depression entirely.

It will be shown in the discussion of the effects of morphine on the respiratory centre that some grounds exist for the belief that the motor functions are depressed by morphine, but this explanation of its action on the cord must be looked upon merely as a preliminary hypothesis to account for the phenomena.

Very small doses may deaden pain without loss of consciousness. Attention weaken. Sudden pain or stim elicit normal response. In big doses as descending [illegible] Large dose [illegible] motor cortex depress

The hypothesis of opposing action on the motor and sensory elements of the cord would explain the different results observed in different classes of animals by assuming that the depressant effects on the motor apparatus are more developed in one class, while in another the stimulation of the receptive apparatus is the predominating feature. It is to be remarked that in all animals the cord is less depressed than in the corresponding stage of chloral poisoning, for if two animals are poisoned, the one with morphine, the other with chloral, until no voluntary movements occur, the reflexes of the one poisoned with morphine are always found more active than those of the other.

The effects of morphine on the **Brain** are no less difficult to account for than those on the cord. In the frog the symptoms of increasing depression correspond to those observed after the removal in succession of the cerebral lobes, the corpora quadrigemina, the cerebellum and the medulla oblongata. In man it is often found that comparatively small quantities are sufficient to deaden or even entirely remove the pain of disease without rendering the patient unconscious. The intelligence is not so acute as normally, but he answers questions and converses freely and may even seem abnormally sensitive to impressions caused by loud noises or bright flashes of light. Animals in this condition may be subjected without resistance to what would ordinarily involve considerable pain, provided the application be not suddenly made. If struck suddenly, however, they react as usual, and remain apparently as sensitive as usual for some time. Morphine then seems to lessen the power of concentrating the attention. As long as any stimulus is of constant strength, be it an internal pain or a noise or light, the morphinized individual remains unconscious of it. On the other hand, a shock is at once perceived, and the lethargy being for the moment dispelled, he reacts to his surroundings for a short time, but is incapable of prolonged attention and soon sinks into stupor again.

Morphine in moderate quantities seems to have but little effect on the irritability of the motor areas of the brain cortex, but in large quantities it lowers and eventually abolishes it. Exner found no alteration in the time elapsing between the perception of a flash of light and a preconcerted movement, while others have found that the reaction to a slight touch was retarded. This would agree with the hypothesis introduced above—the power of summation is lessened and slight stimuli are therefore perceived more slowly, while a stronger impression is perceived and acted upon after the usual interval.

Several observers have investigated the relative sensibility of the skin before and after morphine. The method employed was to measure the smallest distance on the skin at which the person could recognize two points as distinct. In every case it was found that the ability to do this was lessened by morphine, owing to the central depression, the drug seeming not to have any direct action on the sensory organs themselves. No definite histological changes occur in the brain cells or fibres as the effect of morphine.

Slowed breathing from the start - slow - irregular. Resp center affected = hence [illegible] little vol of air inspired - accumulation of CO2 [illegible] sufficiently to act on depressed center, then starts activity + [illegible] or staircase plan then the CO2 disappears from blood, + center's threshold is not maintained we have a down stairs

Respiration.—In man and in most other animals the respiration is slowed by morphine from the beginning (Fig. 18), but in the dog there is often a preliminary stage of rapid, panting breathing, which may, however, be secondary to the emetic and purgative effects. The respiration in man is at first somewhat deeper than usual, but the increase in the depth is seldom sufficient to counterbalance the slowness of the breathing, so that the air inspired per minute is considerably reduced; in the later stages it becomes shallower and is often irregular. This irregularity may have a periodic character, a series of deep respirations being followed by several progressively weaker ones and then by complete inactivity for several seconds. The breathing then recommences with a very slight movement, followed by a series increasing regularly in strength and then again decreasing. This form of respiration (Cheyne-Stokes) is seen in various pathological conditions and has received different explanations, but is probably due to direct action on the respiratory centre. It has been mentioned already that when the animal is once aroused repeated movements are much more easily elicited, and it would seem probable that the accumulation of carbonic acid in the blood during the pause eventually awakens the torpid centre, which causes a small movement. The next movement is larger, owing to the persisting activity of the centre and this continues until, the blood becoming less venous, the stimulus becomes weaker and the cells sink again into their former torpor, to be again resuscitated by the increasing venosity of the blood. Loewy has examined with particular care the condition of the respiratory centre, and found that much larger quantities of carbonic acid than usual were required to increase the volume of the respired air a given degree. His results may indicate that the power of sending out impulses as well as of receiving them is lessened by morphine, while the narcotics of the methane series may perhaps lessen the receptivity of the centre without lessening its power to emit impulses.

FIG. 18.

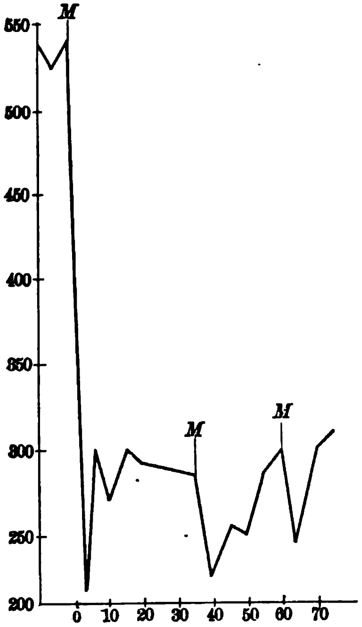


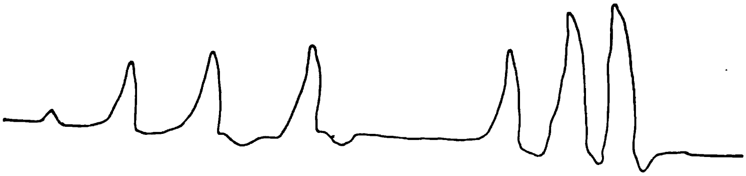
Diagram of the volume of air inspired by a rabbit during morphine narcosis. *M*, injection of morphine. The amount is measured in c.c. along the perpendicular, while the time is measured along the horizontal line. At first about 540 c.c. is inspired in 2½ minutes, but after the injection of morphine, *M*, the volume falls to about 200 c.c. and is maintained at 200–300 throughout the experiment. (After STURSBERG.)

After large doses the respiration becomes gradually slower and

If the sudden shocks (cold etc) fail to arouse consciousness, may stim resp center. CNS depression affects will. later [illegible] & resp. No direct action on circ. B.p. same. Face flushed → cyanotic. Asphyxia slows heart but raises B.p. Net result varies. Some central action

weaker, and often loses its periodic character. Even after consciousness fails to be aroused by the most powerful shocks, some influence may be exerted on the respiratory centre. Thus the sudden application of cold water may cause several deep respirations, although it fails to dispel the stupor, but the respiration finally fails to react to these applications and soon afterwards ceases.

FIG. 19.



Cheyne-Stokes respiration in opium poisoning. The up strokes denote inspiration. (After FILEHNE.)

To sum up the action of morphine on the central nervous system, it produces great depression which is especially marked in the psychical functions, but spreads over the lower parts of the nervous axis and involves sooner or later the respiratory centre. This depression does not seem to affect so much the motor areas as the powers of the will and attention. In mammals the failure of the respiration closes the course of the intoxication, but in the cold-blooded animals a further development of excessive reflex irritability follows which may pass into tonic convulsions. Even in the higher animals and man some indication of this action on the cord may occur, and in the feline group this stimulation involves not only the cord, but also the motor areas of the brain apparently.

Morphine has little direct action on the **Circulation.** The heart is often slightly accelerated at first, perhaps from the slight nausea. The frog's heart is rendered slow and weak by very large quantities of morphine.

The blood-pressure remains high and the peripheral arteries in general show no change of calibre, with the exception of those of the skin, especially of the head and neck, which are dilated, rendering the face flushed and hot; as asphyxia comes on the flush becomes more dusky and cyanotic, but the vessels remain dilated, so that the face is of a bloated, purple color. The dilatation of these vessels, which is due to some obscure central action, has little influence on the general pressure, but causes a sense of warmth in the skin, which is occasionally followed by itching and discomfort. It may account in part for the increased perspiration often observed, although this is doubtless contributed to by other factors. As asphyxia advances, the pulse may become slow, while the blood-pressure ~~varies, either rising from the asphyxial activity of the vasomotor centre~~ or falling from the slowness of ~~the heart. These effects are~~ entirely absent if the blood be suffi~~ciently~~ aërated by artificial respiration, and are, therefore, to be regarded as indirect results of the action on the respiratory centre.

Resp. centre paralyzed before card. - inhib. & v.m. centers affected.
Devoid of local action. Myosis is central. Asphyxia = dilatation.
No action if directly into eye. Retention of urine as sphincter reflex absent.
Secretions, except sweat, lessened. Occasionally vomiting

The selective action of morphine is thus excellently illustrated in its effects on the medulla oblongata, for the respiratory centre is paralyzed before the centres for cardiac inhibition and vaso-constriction are affected to any marked extent.

The peripheral **Muscles** and **Nerves** are also unaffected by morphine in any except overwhelming doses. Even when directly applied to the nerve it has but little effect on the irritability (Waller). When morphine is injected subcutaneously in the frog in large quantities, it lessens the power of the end-organs to transmit impulses, but no such effect is noted in mammals. It is often stated that the sensory terminations are paralyzed by morphine, and solutions are therefore injected into the seat of pain, or liniments are rubbed into the skin over it, but as a matter of fact, morphine seems entirely devoid of any such local action. The sensibility of the skin is lowered by an injection, it is true, but no more so at the point of application than in other parts of the body, so that the action appears to be central.

The **Pupil** undergoes characteristic changes in morphine poisoning. In the great majority of cases in man, the pupil is contracted to pin-point dimensions until just before the final asphyxia, when it dilates widely. In some animals, such as the dog and rabbit, the same effects are seen, while in birds the pupil remains unaffected, and in animals in which morphine causes movement and excitement, it is dilated widely. The action is undoubtedly central, and not due to any local changes in the eye. A number of other drugs produce equally marked contraction of the pupil, but these have the same action when dropped into the conjunctival sac, while morphine has no effect when applied in this way; atropine applied to the conjunctiva at once removes the myosis produced by morphine. The terminal dilatation seen in man is not due to any direct action of the poison, but is a result of the general asphyxia.

As a general rule the **Secretory Glands** seem to be rendered less active than usual by morphine. When it produces nausea it may increase the saliva and the mucus, but these are the usual accompaniments of this condition and cannot be considered due to any special action of the poison. The sweat glands are exceptions to the general rule, however, for slight perspiration is generally observed from the therapeutic action, and profuse perspiration is seen before death in some cases in man from the effects of the asphyxia. The urine does not generally show any distinct alteration after morphine in man, but there is not infrequently retention in the bladder because the sphincter reflex is absent.

The **Alimentary Canal** manifests some distinct changes under morphine, which have not yet been completely explained. In the human subject its injection is occasionally followed by some nausea, which is much more frequently present, however, during recovery from the drug. In the dog and cat nausea and vomiting are almost invariable sequelæ of its application in any form, and from the rapidity with which they follow its subcutaneous injection would seem to be due to

Diarrhoea c̄ dog cat. Constipation in man. Antral + pyloric sphincters
retain food c̄ better absorption slow passage thru g.i. Tends to constipation
Action peripheral in intest. Lessened movements + dil of skin vessels =
lowering of temperature.

its acting on the medullary centre. Small quantities of opium or morphine lessen the sensation of hunger in the human subject, but this is probably to be attributed to central action rather than to any effects on the stomach. Riegel states that in man and the dog the gastric secretion is generally retarded at first but is subsequently increased to a considerable extent. This occurs whether the drug be administered by the mouth or hypodermically and is therefore due to some change induced by it after absorption. The rate of absorption in the stomach and bowel appears to be unchanged by morphine.

The effects on the intestine vary with the dose injected as well as with the species of animal. Very large quantities cause violent peristalsis and repeated evacuation of the bowel in the dog, cat, and, according to some authors, the rabbit, while small doses, on the other hand, are followed by lessened peristalsis and constipation in man and in most animals. Even in poisoning in man, the purgative effect is not observed, and opium and morphine are very extensively used in therapeutics to quiet the movements of the bowel. Magnus found that the constipating action could be elicited after all the nerves to the stomach and bowel were divided, so that it is quite independent of the action on the central nervous system. He states that the passage of food through the stomach is much delayed through a persistent contraction of the sphincter antri pylorici which keeps the contents in the cardiac end, and later of the pyloric sphincter which delays their passage into the duodenum. Their passage through the bowel is also slower than usual, but the chief delay in his experiments occurred in the stomach. This slow emptying of the stomach permits of more complete absorption in the bowel and thus leads to the stools being fewer and of firmer consistence. There is some evidence that in man the evacuation of the stomach is delayed, as in Magnus' experiments on animals, but in all probability the retardation of the passage through the intestine plays a larger part in the constipating effect than he admits. In any case the action is a peripheral one in the wall of the stomach and bowel.

Morphine frequently causes a slight fall in the **Temperature**, which may be explained by the less active movements and the dilatation of the cutaneous vessels; sometimes a slight preliminary rise in the temperature has been seen in man. It is found that animals under morphine react less to an increase in the surrounding temperature than unpoisoned ones; *i. e.*, a normal animal exposed to a high temperature takes measures to prevent its internal temperature from rising above the normal, while, under morphine, these measures are less effective, and the temperature rises more rapidly and to a greater height; this indicates that the temperature centre in the brain is rendered less sensitive.

Metabolism.—The excretion of carbonic acid is lessened during the depression stage, while in those animals in which excitement is produced, it may be considerably augmented from the increased muscular movement. The imperfect respiration leads to an increase in the

CO2, lactic appear in blood in quantity. Glycogen disappears from liver + glycosuria. Excreted in saliva stomach + bowel. Tolerant individual can oxidize enormous quantities - nerve cells become habituated to its presence in blood + react less strongly. Codeine less poisonous, less lasting depressant, but stimulates cord, medulla + lower brain - excitement. Light, unrefreshing sleep. Reflexes increased

lactic acid of the blood and urine and to the disappearance of glycogen from the liver. Sugar may appear in the urine from the same cause.

Excretion.—Morphine is excreted mainly by the digestive tract, in the saliva, stomach and bowel, and is therefore found in large quantities in the fæces even after hypodermic injection. Traces of it occur also in the urine after large doses. It appears in the stomach very soon after injection, a weak reaction occurring after two and one-half minutes according to Alt, but after about an hour no further excretion into the stomach has been shown to occur, although its narcotic action persists much longer. A certain amount of the morphine undergoes partial oxidation in the tissues, and some oxidation products have been said to occur in the urine.

Tolerance.—The continued use of morphine or opium leads to a condition of tolerance, in which enormous doses of the drug are necessary to elicit any effect. Faust has succeeded in producing a similar state in dogs, and finds that much more morphine is oxidized in the tissues in this condition than in untreated animals; for when a normal dog received an injection of morphine, over 60 per cent. of the amount injected could be recovered from the stools, while when a much larger quantity was injected into a tolerant animal, none whatever was found in the excreta. It does not follow that the absence of symptoms from large doses in morphinists is due wholly to the poison being oxidized before it can reach the brain, for Cloetta was able to isolate large quantities from the tissues of animals in which tolerance had been established. It is rather to be inferred that the nerve cells become habituated to its presence in the blood, and cease to react so strongly as in normal individuals, and that in addition the tissues acquire a greater power of oxidizing morphine under these circumstances. The attempt to find "antimorphine serum" has proved fruitless.

Codeine resembles morphine in the general features of its action, although it is much less poisonous. It depresses the brain, and causes an exaltation of the activity of the lower parts of the central nervous system. Its depressant action is not so powerful nor so enduring as that of morphine, however, while the stimulation is more evident and involves not only the cord, but also the medulla oblongata and lower parts of the brain. As has been mentioned already, morphine also stimulates rather than depresses the brain in the feline class, but with codeine this is true also for the dog and to a less extent for man. In the latter small quantities of codeine produce sleep, but this is not so deep and restful as that which follows the administration of morphine, and the patient is liable to be awakened by slight noises, and is restless and often unrefreshed when he awakens. Somewhat larger quantities, instead of inducing deeper sleep, increase the restlessness and cause a considerable exaggeration in the reflex excitability. The respiration is not so much slowed as after morphine, and, according to Winternitz, the excitability of the centre is practically unchanged, while morphine reduces it very considerably. The pupil is slightly contracted during the codeine sleep, but dilates when the no tolerance or constipation: Heroine a resp sedative in cough yet poisonous.

excitement stage follows. Codeine does not seem to produce so great constipation as morphine, and in animals often causes purging and diarrhœa. It is excreted in the urine mainly, and prolonged administration fails to induce tolerance or to promote its destruction in the tissues (Bouma).

Codeine is methylmorphine, and a number of similar compounds have been formed artificially, such as ethylmorphine and amylmorphine. Two of these, ethylmorphine (**Dionine**) and benzylmorphine (**Peronine**) have recently been introduced into therapeutics, but appear to possess no advantages over codeine.

Oxydimorphine ($C_{34}H_{36}N_2O_6$) has been found in opium by some investigators, and has a very weak narcotic action resembling that of morphine.

Heroine is an artificial alkaloid formed from morphine by substituting acetyl for its two hydroxyls, and has attracted some attention recently through its being advocated as a respiratory sedative in cough. It appears to resemble morphine in its general effects, but is said to act more strongly on the respiration and less on the cerebral functions. Thus the respiration is rendered slower with less mental depression than would accompany an equal change elicited by morphine. According to the advocates of heroine, the slowness of the breathing is in part compensated for by its greater depth, so that the actual diminution of the air inspired is not proportional to the decrease in the number of the movements; but this has been disputed and is certainly not invariably true, particularly in man. On the whole the evidence of experimental and clinical observers seems to indicate that heroine deserves a place between morphine and codeine.

Papaverine stands midway between codeine and morphine in its action on the central nervous system, but is a comparatively weak poison. Even in large quantities it has not the soporific action of morphine, nor does it produce the same degree of excitement as codeine. Comparatively small quantities are followed by sleep, but this does not become deeper as the dose is increased. On the contrary, the reflex excitability is augmented, and after very large quantities some tetanic spasm may be elicited, but this seems to be of spinal origin entirely, while that produced by codeine points rather to an affection of the lower part of the brain. Papaverine has more tendency to slow the heart rhythm than either morphine or codeine; it apparently acts directly on the heart muscle and not through the regulating centres. The blood-pressure is little affected by ordinary quantities, however.

Narcotine resembles codeine rather than morphine, but has even less depressant action, especially in mammals. In the frog a short stage of depression is elicited, but this soon gives place to strychnine-like exaggeration of the reflex excitability. In mammals there may be but little appearance of depression, the injection being followed by a condition of excitement immediately—restlessness and tremors with increased reflexes, which eventually lead to convulsions, during which the animal generally succumbs exactly as in strychnine poisoning. The pulse is considerably slower after narcotine injection from a direct action of the drug on the heart. Narcotine is a very much less poisonous body than either morphine or codeine, and very large quantities have been administered repeatedly with little or no narcotic effect. It is a compound of hydrocotarnine, another opium alkaloid, with meconin. **Hydrocotarnine** apparently acts very much in the same way as narcotine, but produces even less depression.

Narceine has attained a certain reputation owing to the statement of Cl. Bernard that it is the most powerful narcotic of all the opium alkaloids. There seems, however, to be no doubt that the preparation he used was very impure, and that narceine itself has little or no action of any kind. It is exceedingly insoluble in water, and its salts are broken up in aqueous solution, so that it is probably absorbed very slowly and imperfectly.

Opium alkaloids Morphine. Papaverine. Codeine. narcotine. thebaine
First a narcotic depressant (causing central resp failure)
Last a stimulant (as strychnine) (" convulsive " ")

Thebaine seems to have practically no depressant action. It sometimes produces some heaviness and confusion in man, but this is accompanied by symptoms exactly resembling those described under strychnine, and it may therefore be considered as belonging to the latter series rather than to that of morphine; it is very much less active than strychnine, however. Thebaine seems to differ from morphine also in its effects on the bowel, for Vamossy finds that it increases peristalsis instead of allaying the irritability. **Laudanine** seems to resemble thebaine very closely in its effects.

The other alkaloids occur in very minute quantities in opium and possess no great interest from the therapeutic point of view. Very little has been done to elucidate their pharmacological action, but those which have been examined seem to produce effects resembling those of the better known members of the group. In frogs, small doses of **Cryptopine** and **Protopine** produce a narcotic condition similar to that following the injection of morphine, but the reflex irritability does not show the same exaggeration afterwards; larger quantities cause complete paralysis of the whole central nervous system and partial paralysis of the terminations of the motor nerves, which gives rise to irregular contractions and relaxations of the muscles when the nerves are stimulated (Hale). In mammals, no depression occurs, but restlessness and eventually convulsions, which do not seem to be of spinal origin but rather suggest a stimulation of the cerebrum and midbrain. The heart is slow and weak, and some depression of the vaso-motor centres is caused by large quantities of the poisons. The respiration does not seem to be depressed, but rather to be accelerated, save by the largest doses. They paralyze the terminations of the sensory nerves on local application in the same way as will be described under cocaine. The action of these two alkaloids on the heart would seem to be further developments of the heart action noted after narcotine and papaverine.

The alkaloids of opium form a series, of which morphine is one, thebaine the other extremity. In morphine the narcotic action is the most striking feature, but as the successive members are taken up, this effect becomes less marked than the reflex stimulation, until in thebaine practically no depression can be made out, and the symptoms resemble those of strychnine exactly. Some of these alkaloids, however, differ in type somewhat from both morphine and thebaine, because the brain itself seems the seat of stimulation, and the convulsions partake more of the character of those produced by picrotoxin than of those of strychnine. Morphine itself possesses this action in the cat, so that these alkaloids do not in reality depart from the general type so completely as might at first appear. The more important members of the group may, therefore, be arranged in the following order, the most depressant standing first and the most stimulant last:

Morphine.
Papaverine.
Codeine.
Narcotine.
Thebaine.
(Strychnine).

In man morphine is much the most dangerous of the opium alkaloids, because death is produced in the narcotic stage through asphyxia. In most animals, however, thebaine, codeine and laudanine are more toxic, because the failure of the respiration does not occur in the stage of depression, but during the convulsions.

Opium + morph. action the same. Other alkaloids of former having little effect.

Opium itself contains besides the alkaloids already discussed, various acids with which they are in combination, meconic, lactic and sulphuric acid, but none of these possess any action of importance. Along with these are found gums, sugars, albumins, wax and the other common constituents of plant juices, but these merely tend to delay the absorption of the active constituents, and cannot be said to play any part in the effects of opium. Of the alkaloids, morphine is present in greatest abundance, and is also the most powerful in its effects. The action of opium is practically identical with that of morphine, the other alkaloids only slightly reinforcing the action of the latter. Opium acts more slowly than morphine, and seems to produce more marked effect on the intestine, in which the mixture of minor alkaloids has also some constipating effect. It is also said to cause less nausea, although this is disputed.

U. S. P. PREPARATIONS.

✓ OPIUM, the dried milky exudation obtained by incising the unripe capsules of Papaver somniferum, yields when moist not less than 9 per cent. of crystallized morphine. Dose, 0.1 G. (1½ grs.). .1G. 1½ gr

✓ OPII PULVIS, dried and powdered opium, yielding 12 per cent. of crystallized morphine. Dose, 0.02–0.1 G. (⅓–1½ grs.).

✓ *Opium Deodoratum,* opium deprived of its odorous principles and of any other bodies soluble in benzin; it contains 12 per cent. of morphine. Dose, 0.02–0.1 G. (⅓–1½ grs.).

✓ *Opium Granulatum,* a coarse powder containing 12 per cent. of morphine. Dose, 0.02–0.1 G. (⅓–1½ grs.).

✓ EXTRACTUM OPII, the dried aqueous extract, contains 20 per cent. of morphine. Dose, 0.015–0.06 G. (¼–1 gr.).

The following preparations contain 10 per cent. of opium or from 1.2 to ~~1.25 per cent. of morph~~ine.

✓ TINCTURA OPII (Laudanum). Dose, 0.3–1 c.c. (5–15 mins.). 0.3–1cc

Tinctura Opii Deodorati. Dose, 0.3–1 c.c. (5–15 mins.).

Vinum Opii, flavored with cinnamon and cloves. Dose, 0.3–1 c.c. (5–15 mins.).

Acetum Opii (Black Drop) is formed by extracting opium powder with dilute acetic acid. Dose, 0.3–1 c.c. (5–15 mins.).

PULVIS IPECACUANHÆ ET OPII (Dover's Powder), 10 per cent. each of opium and ipecac powders. Dose, 0.3–1 G. (5–15 grs.). 0.3–1G

Tinctura Ipecacuanhæ et Opii. Dose, 0.3–1 c.c. (5–15 mins.).

Other preparations of opium generally weaker than the foregoing are:

PILULÆ OPII, each contains 0.065 G. (1 gr.) of opium powder or 0.009 G. (⅐ gr.) of morphine.

Trochisci Glycyrrhizæ et Opii, each contains 0.005 G. ($\frac{1}{12}$ gr.) of opium.

TINCTURA OPII CAMPHORATA (Paregoric) contains four parts of opium per ~~thousand,~~ along with benzoic acid, camphor, oil of anise and glycerin. Dose, 4–15 c.c. (1–4 fl. drs.) for an adult, 0.3–1 c.c. (5–15 drops) for a child. 4–15cc child .3–1cc

Mistura Glycyrrhizæ Composita (Brown Mixture) is formed from liquorice, syrup, acacia, wine of antimony, spirits of nitrous ether and camphorated ~~tincture of opium, and~~ contains only about 1 part of opium in 2,000. Dose, 8 c.c. (2 fl. drs.).

Alkaloids:

MORPHINA ($C_{17}H_{19}NO_3 + H_2O$), colorless crystals without odor but with a

.005 - .03 bitter taste, practically insoluble in water and only slightly soluble in alcohol. Dose, 0.005–0.03 G. ($\frac{1}{12}$–½ gr.).

1/12 - 1/2 gr

Morphinæ Hydrochloridum.
Morphinæ Sulphas.
Morphinæ Acetas.

Of these salts the hydrochlorate and sulphate are the most important, as the acetate tends to decompose on keeping. The hydrochlorate and sulphate are soluble in about 21–24 parts of water, less so in alcohol. They form white, silky crystals with a bitter taste. Dose, 0.005–0.03 G. ($\frac{1}{12}$–½ gr.).

Pulvis Morphinæ Compositus (Tully's Powder) is a mixture of liquorice powder, camphor and morphine sulphate, in which the latter is contained to the amount of 1½ per cent. Dose, 0.3–1 G. (5–15 grs.).

1/4 - 1 gr Codeina ($C_{18}H_{21}NO_3 + H_2O$), white or nearly transparent crystals with a faintly bitter taste, soluble in 80 parts of water and in 1.6 parts of alcohol. Dose, 0.015–0.6 G. (¼–1 gr.).

1/2 gr Codeinæ Phosphas. 2 pts water
Codeinæ Sulphas.

These salts of codeine form white needle-shaped crystals with a bitter taste. The phosphate is soluble in about 2 parts of water, the sulphate in 30 parts. Dose, 0.03 G. (½ gr.).

B. P. Preparations.

Opium, the juice obtained by incision from the unripe capsules of Papaver somniferum, inspissated by spontaneous evaporation. When dried it contains 9½–10½ per cent. of anhydrous morphine, and it is therefore weaker than the corresponding preparation of the U. S. P. Dose, ½–2 grs.

Extractum Opii contains 20 per cent. of morphine. Dose, ¼–1 gr.

Tinctura Opii, Laudanum, contains ¾ per cent. of morphine, or about 1 gr. of opium in 15 mins. Dose, 5–15 mins. for repeated administration; for a single administration 20–30 mins.

Tinctura Opii Ammoniata is formed of laudanum, benzoic acid, oil of anise and ammonia. It contains about ⅒ per cent. of morphine or nearly 5 grs. of opium in the fluid oz. Dose, ½–1 fl. dr.

Tinctura Camphoræ Composita, Paregoric or Paregoric Elixir, resembles the foregoing in composition except that camphor is substituted for ammonia and that the laudanum is reduced so that only one part of morphine is contained in 2,000 of paregoric or ¼ gr. of opium in each fl. dr. Dose, ½–1 fl. dr.

Pulvis Opii Compositus contains 10 per cent. of opium along with pepper, ginger, caraway and tragacanth. Dose, 2–10 grs.

Pulvis Ipecacuanhæ Compositus, Dover's Powder, contains 10 per cent. each of opium and ipecacuanha in powder. Dose, 5–15 grs.

Pulvis Kino Compositus contains 5 per cent. of opium along with kino and cinnamon. Dose, 5–20 grs.

Pulvis Cretæ Aromaticus cum Opio contains 2½ per cent. of opium along with aromatic chalk powder. Dose, 10–40 grs.

Pilula Plumbi cum Opio contains 12½ per cent. of opium along with lead acetate. Dose, 2–4 grs.

Pilula Saponis Composita, contains 20 per cent. of opium. Dose, 2–4 grs.

Pilula Ipecacuanhæ cum Scilla is formed from Dover's powder and squills, and contains about 5 per cent. of opium. Dose, 4–8 grs.

Suppositoria Plumbi Composita, each contains 3 grs. of lead acetate and 1 gr. of opium.

Morphinæ Acetas ($C_{17}H_{19}NO_3,C_2H_4O_2,3H_2O$), a white crystalline or amorphous powder almost entirely soluble in 2½ parts of water and in 100 of alcohol, ⅛–½ gr.

[illegible] — a specific. [illegible]
tolerance so increasing dosage. Small dose will lessen pain. Antipyretics
lessen pain in neuralgia + headache, without danger of habit formation.

MORPHINÆ HYDROCHLORIDUM ($C_{17}H_{19}NO_3,HCl,3H_2O$), acicular prisms of a silky lustre, soluble in 24 parts of cold water, one part of boiling water, or 50 of alcohol. Dose ⅛–½ gr.

Morphinæ Tartras ($(C_{17}H_{19}NO_3)_2C_4H_6O_6,3H_2O$), a white powder consisting of fine nodular tufts of acicular crystals, soluble in 11 parts of cold water, insoluble in alcohol. Dose, ⅛–½ gr.

LIQUOR MORPHINÆ HYDROCHLORIDI, 1 per cent., 10–60 mins.

INJECTIO MORPHINÆ HYPODERMICA contains 5 per cent. of the tartrate. Dose by subcutaneous injection, 2–5 mins.

SUPPOSITORIA MORPHINÆ, each contains ¼ gr. of morphine hydrochloride.

TROCHISCUS MORPHINÆ, each contains $\frac{1}{36}$ gr. of morphine hydrochloride.

Trochiscus Morphinæ et Ipecacuanhæ, each contains $\frac{1}{36}$ gr. of morphine hydrochloride with $\frac{1}{12}$ gr. of ipecacuanha root.

Tinctura Chloroformi et Morphinæ Composita corresponds to the patented chlorodyne and contains 1 per cent. of morphine hydrochloride, along with chloroform, prussic acid, capsicum, cannabis indica, oil of peppermint and glycerin. Dose, 5–15 mins.

CODEINÆ PHOSPHAS ($(C_{17}H_{18}(CH_3)NO_3,H_3PO_4)_2,3H_2O$), white crystals with a slightly bitter taste, soluble in 4 parts of water, much less soluble in alcohol. Dose, ¼–2 grs.

SYRUPUS CODEINÆ, one fluid drachm contains ¼ gr. of codeine phosphate. Dose, ½–2 fl. drs.

Therapeutic Uses.—Opium is one of the most important and most extensively used drugs in the pharmacopœias at the present day as in the past. Of late years the crude drug has been largely replaced by morphine, but the action is the same, and although morphine is preferable in most cases, opium is still specially indicated for certain purposes. In almost any disease, conditions which are favorably influenced by morphine may present themselves, and these conditions alone can be discussed here.

Pain.—As has been repeatedly mentioned, opium or morphine has a special analgesic action which is not shared by its modern rivals of the methane series, and which justifies the celebrated dictum of Sydenham that without opium few would be callous enough to practise therapeutics. The general statement may suffice that severe pain indicates opium. Even where the disease itself is one which would in ordinary circumstances contraindicate it, it must be always taken into consideration whether the relief of the pain and its attendant restlessness may not counterbalance the disadvantages of the narcotic. At the same time the danger of inducing the craving for morphine cannot be forgotten, for the use of morphine to subdue pain is perhaps the most fruitful cause of the habit. It is often found that comparatively small quantities of opium are sufficient to remove or at any rate to dull pain, but after repeated doses the quantity has to be increased owing to tolerance being attained. Some forms of pain are relieved by the members of the antipyrine series, but these are less certain and more limited in their action than morphine. On the other hand the antipyretics often relieve pain without inducing sleep, and in this possess a great advantage over opium in the treatment of headache, neuralgia and similar conditions.

When insomnia is due to pain. When to brain excitability mania etc give chloral or a combination.
tetany, epilepsy (bromides). To rest patient good in acute fevers.
For resp effects in cough & dyspnoea, asthma (n.b. where much expectoration!)

Codeine (resp depression - little cerebral depression) + expectorant for dry cough.

Sleeplessness.—Opium was formerly the only drug used to induce sleep, but since the discovery of chloral and its congeners it is used less frequently. These fail entirely to replace it, however, where the sleeplessness is due to pain, while, on the other hand, they are more efficacious in some conditions of excitement. Not infrequently opium and chloral are prescribed together for this purpose, and the combination acts more efficiently than either of the drugs alone. Each is, of course, prescribed in considerably smaller amount than if administered separately. Opium is less efficient than chloral when there is apparently an increased activity of the motor functions of the brain, as in wild delirium and mania, and sometimes seems to increase the excitement even, but this general statement is subject to numerous exceptions, and morphine is still largely used in many such disorders. In the true convulsive diseases, such as tetanus, epilepsy and chorea, chloral is preferable. The beneficial effect of morphine in many acute febrile conditions is undeniable, and, as in the case of alcohol, is due to its lessening the pain and discomfort of the patient and inducing rest. A good deal of difference of opinion exists as to the advisability of administering opium or morphine in these conditions, and there is no question that the routine treatment of fever by narcotics is to be deprecated; but on the other hand, the restlessness and discomfort may in itself aggravate the disease, and morphine is distinctly indicated under these circumstances.

The preparations chiefly used to relieve pain and promote sleep are the extracts, laudanum, opium pill, or compound soap pill, and the morphine salts and their solutions, including the hypodermic injection.

In **Respiratory Disorders** opium and morphine are largely used for their effects on the centre. Where it is desirable to lessen its irritability, as, for example, in excessive cough and dyspnœa, opium may be indicated. On the other hand, when there is a profuse expectoration, the irritability of the centre cannot be lowered without danger, and opium is contraindicated. Opium gives relief in cases of asthma, but there is always danger of inducing the habit.

Opium is often combined with expectorants in the treatment of cough, and a large number of suitable preparations are provided in the pharmacopœias, such as paregoric, Dover's powder and other preparations containing ipecacuanha, liquorice mixture, the compound morphine powder (U. S. P.), the ammoniated tincture, the compound tincture of chloroform and morphine, the pills of ipecacuanha and squill (B. P.), the lozenges and the codeine preparations. The object of combining expectorants with opium is to allay excessive coughing; the opium reduces the excitability of the centre, while the expectorant causes a secretion of mucus in the respiratory passages and thus protects the irritated mucous membrane. The combination is indicated only in dry cough with little expectoration, and when there is abundant sputum to be removed by coughing the treatment may be harmful. Codeine is often preferred to morphine in these cases, because it reduces the excitability of the respiratory centre with less marked

In Peritonitis & I. disorders 1) allays restlessness & pain. 2) intestinal movements. Opium has better effects as stays longer in bowel (but action central?) In lead colic lessens pain without absolute constip. In diarrhoea perforation & hemorrhage (allays restlessness) 4-5. In vomiting. In nervous patients preceding operation. Or ¼ gr + 1/200 hyoscine = complete anaesthesia. Useful in malaria (& quinine)

cerebral depression. This is also true of the new artificial alkaloids, heroine and dionine, which have enjoyed some popular reputation in late years. Impartial investigators of these drugs have generally failed to obtain better results from them than from codeine and morphine, and they are in no respect superior to the older and unpatented alkaloids.

In Peritonitis and Intestinal Disorders opium is indicated doubly; first, for its general action in allaying pain and restlessness; and secondly, for its special action in lessening the movement of the intestine. Opium is preferable to morphine for these purposes because it lies longer in the bowel, and therefore evolves a stronger action there than on the rest of the economy, and also because the minor alkaloids have some constipating effect. In colic, especially lead colic, it often relieves the pain without increasing the constipation and seems to allay the spasm of the bowel without stopping entirely its peristalsis. In diarrhœa opium may be given to check the excessive peristalsis, though in the severer forms of dysentery it generally fails to have this effect, and in septic purging is rather to be avoided. In perforation and hemorrhage from the bowel, opium is the most efficient of all remedies, as it allows adhesions or clots to be formed by checking movements of the intestine, which would provoke further leakage.

The B. P. offers a number of preparations specially designed for use in intestinal disorders and especially in diarrhœa, such as the compound kino powder, the compound chalk powder, the lead and opium pill, and the compound lead suppository and morphine suppository. Instead of these the tincture, extract or other simple preparation may, of course, be used.

In **Hæmorrhage**, where the bleeding point cannot be reached, opium or morphine is most valuable. This is not from any direct effect on the vessels or blood, but because it allays the restlessness which follows the loss of large quantities of blood and thus allows the blood to clot in the ruptured vessel. The same preparations are suitable here as for pain.

In **Vomiting** morphine is sometimes used in small quantities, but it seems doubtful whether with any benefit.

Morphine is not infrequently given as a preliminary to general anæsthesia in nervous patients (¼ gr.), and in recent years operations have often been performed under morphine and hyoscine (scopolamine) alone. For this purpose ⅙ gr. (10 mgs.) of morphine and about 1/200 gr. (0.3 mg.) of hyoscine are injected an hour and a half before the operation and again half an hour before it. The anæsthesia induced is often sufficient, and, if necessary, a few drops of ether or chloroform may be inhaled to complete it.

Opium has been used instead of quinine in **Malaria**, and though it cannot be said to replace the latter, has a distinct effect in some cases apparently. Of course, symptoms may arise in malaria as in other diseases in which opium is specially indicated, but apart from this, cases of malaria of old standing seem to be benefited by opium with or without quinine.

Codeine lessens [illegible] glycosuria & not so much constip. as with morphine. Dover's powder for diaphoresis = dil of skin vessels. Locally n.g. Codeine less efficient in allaying pain, less habit. OK for melancholia insomnia - 1 drop of laudanum may kill a small child [illegible] contraindic. also pt with weakness, cerebral congestion, poor appetite. Not harmful in Bright's as not excreted by kidney.

Opium or morphine has sometimes been used in **Diabetes** with good effects; for though the glycosuria seldom disappears under its use, it is lessened in some cases (Kaufmann). Codeine has been advised instead of morphine in this disorder, as it is less likely to cause constipation and gastric disturbance.

Lastly, opium is used as a **Diaphoretic**, and for this purpose it is generally combined with ipecacuanha and prescribed as Dover's powder. Although in itself it has little or no diaphoretic action, opium may augment the effects of ipecacuanha through dilating the skin vessels. Opium and its alkaloids have no effect applied to the skin, and the plasters, ointments and other similar preparations are quite superfluous.

Codeine is much less often used than morphine in therapeutics. It is of comparatively little value in allaying pain or excitement, but has been found of benefit in the sleeplessness of melancholia. It is used not infrequently as a sedative in cough, and, as has been stated, in diabetes. There is less liability to the formation of the codeine habit, and it has been suggested as a substitute for morphine in morphinomania, but has not proved efficient in this condition.

Opium and morphine are contraindicated in very young children, in whom even minute quantities often produce the most alarming symptoms of poisoning. Even one drop of laudanum is said to have been fatal to a child under one year of age. In great weakness, especially in cases where the respiration is barely sufficient to aërate the blood, or where profuse expectoration is present, morphine has to be administered with the greatest care. In cerebral congestion and meningitis the opiates are generally contraindicated. It must be remembered also that both opium and morphine are liable to disturb the digestion and to cause nausea and want of appetite, and that these may prevent their use in cases in which they would otherwise be suitable. In some persons opium invariably causes nausea and vomiting, either soon after its administration or while its effects are passing off. For this idiosyncrasy morphine may be substituted for opium, although this is often equally nauseating, or chloral and bromides may be prescribed with opium to prevent the unpleasant after-effects. Not infrequently, however, opium has to be avoided entirely. In all chronic painful diseases opium or morphine has to be given guardedly, on account of the risk of the formation of the opium habit; the patient ought to be kept in ignorance of the drug used as far as possible, and it should be alternated with others. Of course, in cases of incurable, hopeless disease, where life can only last a comparatively short time and is attended by severe suffering, this objection does not hold, and it may be necessary to administer morphine without stint and in ever-increasing quantity.

Morphine and opium are often said to be contraindicated in Bright's disease of the kidney. This seems to be due to the belief that morphine is excreted in the urine, which has now been shown to be erroneous. There seems no reason to believe that morphine is harmful

Acute poisoning – breath – pinpoint pupil. Stomach tube repeatedly (several times). Dashes of cold water, elec., flipping with towels to arouse resp. Artif. resp. (elec or mech) for hours. Caffeine. Small amts of atropine stim. medulla, large dose depresses. Alcohol stim. resp. reflexly, but depresses resp directly. KMnO4 oxidizes in stomach, but worthless after absorption.

in these conditions, and in some forms of uræmia it has even been of considerable benefit.

Acute Poisoning with morphine or opium is one of the commonest forms of intoxication, with the exception of the alcoholic. It is often difficult to diagnose from other forms of unconsciousness, but the extreme contraction of the pupils gives a clue, as a general rule, and if opium has been used, the breath often has the characteristic odor.

The treatment is immediate evacuation of the stomach, whether the drug has been taken by the mouth or not, as even when injected hypodermically it is excreted into the stomach and may be reabsorbed. Emetics may be employed for this purpose, but often fail of effect owing to the depression of the medullary centres, so that where possible a stomach tube ought to be used in preference. The stomach should be thoroughly washed out at intervals, in order to remove every trace of the drug as it is excreted. As the respiration begins to fail, it is to be encouraged by irritation of the skin, either by dashing cold water on it, by the electric current, or by flipping it with towels. The violent flagellation formerly advocated with the view of encouraging the respiration, served also usually to exhaust the nervous energy both of patient and attendant. When these means fail to keep up the natural breathing, it is necessary to resort to artificial respiration, either electrical or mechanical, and this ought to be continued as long as the heart continues to beat. Enormous doses of morphine and opium have been recovered from under this treatment. Numerous drugs have been advocated in acute morphine poisoning, and of these caffeine administered either hypodermically or in the form of strong coffee by the stomach seems the most satisfactory. A long controversy has been carried on as to whether atropine is to be considered an antidote to morphine and used in these cases. It is a stimulant to the medullary centres, and may, therefore, be used in small quantities; but large quantities, such as have been advised by some authorities, are undoubtedly harmful, as atropine itself paralyzes the respiration when given in sufficient amount. Bashford states that the best effects are to be expected from about 1.5 mg. (1/40 gr.) of atropine and that more than this increases the danger of respiratory failure. In discussing this question too great weight has been laid on the results of animal experiment, which is not convincing in this case, as the effects of morphine are so different in man. Caffeine seems certainly more indicated than atropine, for it is scarcely possible to paralyze the respiratory centre with the former, which stimulates it equally strongly. Alcohol has been advised also, and as far as its local action is concerned, it may increase the respiration, but its direct action on the respiratory centre is similar to that of opium. Of late years permanganate of potash has been advised in case of morphine poisoning, because the poison is oxidized by it. A certain amount of poison in the stomach may be destroyed in this way, but the portion absorbed is unaffected by the permanganate, and the method is less efficacious than the prompt and repeated use of the stomach tube. The hypodermic injection of permanganate is, of course, entirely useless.

Smoked in East – laudanum or pills in West – or by hypo. Not
stim. but depresses sensibility. Diag. nervous, inefficient, poor gait,
tremors contracted pupil, nutrition poor ditto appetite. Constipation
alternates with diarrhoea. Leads to melancholia & dementia. Test by giving

suspected a normal dose
Will & self control paralyzed.

Chronic Opium or Morphine Poisoning is a not infrequent condition, and, unfortunately, seems to be increasing rapidly. Among Eastern nations, especially in China and India, opium is smoked, and some of the morphine is carried over in the smoke and absorbed from the ~~respiratory tract.~~ This habit is rare in European peoples, among whom the drug is taken by the mouth, generally in the form of laudanum or of pills, or is injected ~~hypodermically as~~ morphine hydro~~chlorate or sulphate.~~ Of the three methods the first seems to be the least harmful, for in some parts of China the majority of the adult population seems to indulge in it without the serious results which are met with in the Western opium-eaters and morphinomaniacs. This result may be due in part to race, or to the fact that the opium-smoker never attains to the immense doses taken daily in the cases of the habit met with in Europe and America. In the beginning the quantity used is small, but as tolerance is attained, ever larger quantities are required to produce any effect, until, as De Quincy states in his "Confessions of an Opium-eater," 320 grains of opium may be required to stay the craving. The effects are generally described as stimulant, but it seems possible that they consist rather in depression of the sensibility, by which the unfortunate patient becomes unconscious of the miseries of his condition, and may accordingly be able to perform his duties and maintain appearances better than when deprived of the poison. The symptoms of the opium habit are exceedingly indefinite, and the diagnosis is often almost impossible. The statements of the patient ought not to be taken into consideration, because these unfortunates seem to have lost all idea of honor and truthfulness. As a general rule they are nervous, weak in character and wanting in energy, and utterly unfit for work unless when supplied with the drug. The pupils are often contracted, the heart sometimes irregular, and tremors and unsteadiness in walking may be apparent. The appetite is bad and a considerable loss in weight occurs, and the movements of the bowels are irregular, constipation alternating with diarrhœa. Eventually melancholia and dementia may follow the prolonged use of opium, and especially of morphine. Some continue the habit for many years, however, and it would seem with comparative immunity. If morphine is injected habitually, evidence may be obtained from the small needle marks on the front of the body, which often give rise to multiple abscesses of small size from carelessness in the disinfection of the syringe. When other evidence fails, it may be necessary to give a moderate dose disguised in some unusual way and to observe if it induces sleep; in habitual users the ordinary dose will have little or no effect.

The treatment of chronic morphine poisoning is not very promising. The will and self-control would seem completely paralyzed in many cases, and although the patient wishes to be freed from his enemy, he seems utterly unable to withstand the craving. The only means of treatment which promises success in most cases is the strict régimé of an asylum or retreat, where the patient is kept under constant super-

Immediate removal = misery & dangerous depression.
Relapses common. Prognosis unfavourable. Retreat for watching
Drugs useless. Try to switch over to codeine.

vision. The immediate removal of the drug often produces such intense misery and depression as to seem actually dangerous; but the withdrawal ought not to be too gradual, and ought to be complete after two or three weeks at the most. The patient has to be watched carefully for long after he has apparently recovered, as relapses are exceedingly common.

The morphine habit has often been combated by the substitution of other drugs, such as cocaine, but the result generally has been that a new and even more dangerous habit has been substituted for, or often merely grafted on, the original. Numerous drugs have been proposed for the cure of morphinomania, but none of them seems to have the slightest effect.

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Minor Drugs of the Opium Series.

In some other members of the poppy family (Papaveraceæ), alkaloids are found which bear a close resemblance to those of opium. These are *Chelidonine, α-, β-* and *γ-Homochelidonine, Chelerythrine* and *Sanguinarine; Protopine* is also found in a number of other papaveraceæ. These alkaloids are met with in very small quantities in various plants, of which Sanguinaria Canadensis (Bloodroot) and Chelidonium majus (Celandine) are the best known.

Chelidonine and *a-homochelidonine* resemble morphine in their effects on the central nervous system, but have even less stimulant effect. In the frog no secondary increase in the reflex irritability is produced, but in some mammals a slight stimulation of the spinal cord may be caused. They have the same effect as protopine and cryptopine on the nerve-ends and heart, and like them produce insensibility of the skin and cornea when applied locally through paralyzing the terminations of the sensory nerves. The heart is slowed, partly owing to stimulation of the inhibitory centres in the medulla, and partly through direct action on the cardiac muscle.

Sanguinarine has very little depressant action, but causes tetanus and wild excitement, so that as far as its action on the central nervous system is concerned, it deserves a place between codeine and thebaine of the morphine series. It possesses the same peripheral action as protopine, however, and the heart is slowed through direct affection of the muscle. Sanguinarine paralyzes the peripheral sensory endings when applied locally, but this paralysis is preceded by a stage of irritation. It causes violent peristalsis of the bowel, and increases the secretion of saliva.

β-homochelidonine resembles protopine and cryptopine closely in its effects, causing the same stimulation of the lower parts of the brain with very slight effects on the intellectual powers, slowing the heart through its muscular action and paralyzing the sensory terminations.

Chelerythrine paralyzes the central nervous system without any preliminary increase in the reflex irritability, possesses the peripheral action of protopine and cryptopine, and first irritates and then paralyzes the sensory terminations.

None of these alkaloids have been used in therapeutics, and there would seem to be no indication for them that is not as well met by opium or morphine. None of the plants containing them have been used to any great extent, although Sanguinaria Canadensis was formerly occasionally prescribed as a nauseating expectorant and emetic. The "sanguinarine" of commerce is generally a mixture of the alkaloids with other constituents, and, like the other preparations of the plant, might well be dispensed with.

U. S. P. PREPARATIONS.

Sanguinaria, the rhizome of Sanguinaria Canadensis, bloodroot, collected in autumn.

Tinctura Sanguinariæ, 1 c.c. (15 mins.).
Fluidextractum Sanguinariæ, 0.1 c.c. (2 mins.).

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Anhalonium.—A number of alkaloids, some resembling morphine, others strychnine in their effects on animals, have recently been isolated from different members of the Anhalonium genus (Fam. Cactaceæ). In Mexico, and along the southern boundary of the United States, where those plants are indigenous, some of them are used as narcotics in the religious rites of the Indians and are known as Pellote, Peyotl, or Muscale or Mezcal Buttons. The symptoms arise for the most part from the cerebrum and differ from those of opium and cannabis indica in the frequency with which color visions are induced, these consisting in constantly shifting flashes of brilliant tints. Mezcal eating does not induce merriment like cannabis nor sleep like morphine but depression of some functions is indicated by the imperfect coördination of the movements, the retarded perception and the errors in the estimation of time. The exaltation seems to be caused for the most part by

Hydrastine ~~[illegible]~~ reflex excitability ↑ · heart slower & weaker · V.M. [illegible] then depressed
convulsions
directly contracts uterus — rhythmic or tetanic

one of the alkaloids, mezcaline. Very large doses have induced unpleasant symptoms through depression of the respiration. Anhalonium and pellotine, one of its alkaloids, have been used as narcotics in a few cases of insomnia.

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V. HYDRASTINE AND HYDRASTININE.

Another alkaloid which is closely related to those of opium chemically and pharmacologically, is *Hydrastine,* which occurs in the Hydrastis Canadensis (Golden Seal) along with *Berberine* and *Canadine.*

Hydrastine ($C_{21}H_{21}NO_6$), when exposed to oxidizing agents such as potassium permanganate, is decomposed into opianic acid and *Hydrastinine* ($C_{11}H_{13}NO_3$), another alkaloid. Narcotine ($C_{22}H_{23}NO_7$), the opium alkaloid, undergoes a similar decomposition into opianic acid and *Cotarnine* ($C_{12}H_{15}NO_4$). Hydrastine and narcotine differ only in a hydrogen atom of the former being substituted by — OCH_3 in the latter, and a similar relation exists between hydrastinine and cotarnine. All four are derivatives of isoquinoline. The action of hydrastis is similar to that of hydrastine, the berberine and canadine having little effect; the latter is as poisonous as hydrastine, but is present only in very small quantities in the plant.

Action.—Hydrastine causes in frogs an increase in the reflex irritability and eventually tetanus exactly resembling that produced by strychnine, and like it terminating finally in paralysis. The heart is rendered slow and weak, partly by the central stimulation of the inhibitory apparatus and partly by direct action on the muscle fibres.

In mammals the pulse is slowed by comparatively small quantities, while somewhat larger doses cause general feebleness, tremor, dyspnœa, and incoördination in the movements. Very large quantities elicit clonic and then tonic convulsions and tetanus, during which the respiration ceases. The pulse is slowed at first from stimulation of the vagus centre, is afterwards quickened from its paralysis, and still later becomes slow again from direct action on the cardiac muscle. The blood-pressure rises from constriction of the arterioles but afterwards falls, partly from their dilatation and partly from the weakness of the heart; the constriction of the arterioles is due to stimulation of the vasomotor centre in the medulla. Hydrastine injected intravenously arouses the uterus to contractions, which are sometimes rhythmic in character, but sometimes assume a prolonged tetanic form. This also occurs in the excised organ, so that the alkaloid must act directly on it and not through the central nervous system.

Hydrastine is excreted as such in the urine. When it is administered for some time, a cumulative action is said to be developed.

Canadine in small quantities produces depression and drowsiness followed by complete recovery without further symptoms. In larger quantities v. Bunge found that it caused a short stage of excitement, which was followed by depression and paralysis of the central nervous system. It has little or

Canadine a depressant to C.N.S. = weakness etc. ↑ peristalsis
Hydrastinine derived from hydrastine no CNS motor depression. I + vm. stim. which some say will stop haemorrhage. Locally or circ. uterus contracts
A stomachal bitter
(ref. from uterus (ergot better))

Alterative for m.m. catarrhs.

no effects on the mammalian circulation when administered in ordinary doses, but very large quantities cause weakness and arrhythmia of the heart. Its injection is followed by violent peristalsis of the intestine and diarrhœa. Canadine is present in only very small quantity in the Golden Seal and has apparently little importance in therapeutics.

Hydrastinine, an artificial alkaloid formed from hydrastine, has of late years attracted a certain amount of attention from its alleged power of arresting hemorrhage. It seems to differ from hydrastine in causing no marked disturbance of the centres of motion and feeling save in enormous doses, which paralyze the nervous system, and, in the frog, the terminations of the motor nerves in muscle (Santesson). On the other hand, its action on the medulla oblongata resembles that of the parent substance. The heart is slowed somewhat by small doses, apparently from stimulation of the vagus centre, and the arterial tension rises further than after hydrastine. Unlike the latter, however, hydrastinine causes a very prolonged augmentation of the blood-pressure, because it does not tend to depress the heart to the same extent as hydrastine. In fact, several authors believe that it increases the efficiency of the heart movements from action on the muscle, although the pulse may be somewhat slowed by stimulation of the inhibitory centre. After very large quantities, the pulse is often extremely rapid from paralysis of the inhibitory centre.

The cause of the increased arterial tension is still undecided. There seems to be undoubted stimulation of the vasomotor centre, but according to some writers, the peripheral vessels are contracted by direct action on the walls as well. This statement seems open to question, however, none of the experiments on which it is founded being altogether satisfactory. Hydrastinine produces rhythmical contraction of the uterus, and even abortion in animals; as this occurs in the excised uterus, the action appears to be directly on the organ itself and not through the central nervous system. The uterine vessels undergo constriction like those of the rest of the body, and this may stop hæmorrhage.

Archangelsky states that a 10 per cent. solution of hydrastinine applied locally causes dilatation of the pupil, which reaches its maximum in two to three hours, and lasts for twelve to fifteen hours.

PREPARATIONS.

Hydrastis (U. S. P.), **Hydrastis Rhizoma** (B. P.), the rhizome and roots of Hydrastis Canadensis, Golden Seal.

Fluidextractum Hydrastis (U. S. P.), 1–4 c.c. (15–60 mins.).

Extractum Hydrastis Liquidum (B. P.), 5–15 mins.

Glyceritum Hydrastis (U. S. P.), 1–4 c.c. (15–60 mins.).

1-4 cc ✓ *Tinctura Hydrastis* (U. S. P., B. P.), 1–4 c.c. (15–60 mins.).

Hydrastina (U. S. P.), white, bitter, almost insoluble crystals. 10 mgs. (⅙ gr.).

Hydrastininæ Hydrochloridum (U. S. P.), 0.03 G. (½ gr.), given in solution hypodermically or by the mouth, or in pills or tablets.

Therapeutic Uses.—Hydrastis has been used as a stomachic bitter and the large quantity of berberine contained in it would seem to give

Cannabis – Indian hemp – Hashish – smoked, drunk or confection
100,000,000 people

it a place along with the simple bitters. It has also been credited with some obscure action on the mucous membranes when locally applied, through which it is said to benefit many forms of catarrhal inflammation. For this purpose the glycerite may be used. Besides various conditions in which its use was attended by doubtful success, it has been used in hæmorrhage from the uterus; but for this purpose hydrastinine ought to be preferred, as it causes a much greater constriction of the peripheral vessels than hydrastine, and acts less on the heart. The conditions in which it is indicated seem to be moderate hæmorrhage; for example, hydrastinine is of value in excessive menstrual flow, while in post-partum hæmorrhage it seems to have little effect. Hydrastis and its alkaloids have not attained any assured position in therapeutics, for at best it can only be considered an inferior substitute for ergot, which has a much more decided action on the vessels and the uterus.

Cotarnine has been introduced under the name of *Stypticine* and *Styptol* as a substitute for hydrastinine in uterine hæmorrhage. Dose, 0.02–0.03 G. ($\frac{1}{3}$–$\frac{1}{2}$ gr.). It resembles hydrastinine in its general action and has received some recommendation at the hands of gynecologists.

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VI. CANNABIS INDICA.

The hemp plant possesses no pharmacological interest when grown in temperate regions, but when cultivated in warm climates as in India, Egypt or the southern United States, it develops products which induce marked derangements of the central nervous system. The Indian plant was formerly supposed to be a distinct species, but differs so little from the European form that botanists now consider them merely varieties. The old name of Cannabis Indica has, however, been retained in medicine. Its introduction into Western medicine dates only from the beginning of last century, but it has been used as an intoxicant in Asiatic countries and in Africa since unknown time, and under the names of *Hashish, Bhang, Ganja, Charas* or *Churrus,* is habitually indulged in by some one or two hundred millions of mankind. Some of the preparations are smoked either alone or mixed with tobacco; others form an intoxicating drink, while in others it is mixed with sugar or honey and taken as a confection.

The active principle of Indian hemp has been found by Wood, Spivey and Easterfield to be a red oil or resin boiling at a high temperature, which they

Cannabinol. Varies as plant & [illegible] dreamy state, judgement lost, imagination increased — Amorous. happiness, most pleasant. Reasonable when aroused. First stage may be absent in Europeans & may pass directly into sleep. Awakens refreshed & no depression

term *Cannabinol;* this was found by Marshall to induce the typical effects of cannabis indica in man and animals. Fränkel states that cannabinol is a phenolaldehyde of the formula $OH \cdot C_{20}H_{28}COH$.

Symptoms.—The effects of cannabis indica are chiefly due to the changes in the central nervous system, in which it induces a mixture of depression and stimulation similar to that seen occasionally under morphine. Its action is much less constant, however, and seems to depend very largely on the disposition and intellectual activity of the individual. The preparations used also vary considerably in strength, and the activity of even the crude drug seems to depend very largely on the climate and season in which it is grown, so that great discrepancies occur in the accounts of its effects. Soon after its administration, the patient passes into a dreamy, semiconscious state, in which the judgment seems to be lost, while the imagination is untrammeled by its usual restraints. The dreams assume the vividness of visions, are of boundless extravagance, and, of course, vary with the character and pursuits of the individual. In the eastern races they seem generally to partake of an amorous nature. The true believer sees the gardens of paradise and finds himself surrounded by troops of houris of unspeakable beauty, while the less imaginative European finds himself unaccountably happy and feels constrained to active movement, often of a purposeless and even absurd character. Ideas flash through the mind without apparent continuity, and all measurement of time and space is lost. True hallucinations may appear, but are often absent, the chief features of the action being merriment, comfort, well-being and self-satisfaction. Often less pleasant thoughts obtrude themselves, however, such as the fear of impending death or of some imminent indefinite danger. During this period the consciousness is not entirely lost, for the patient often feels that his dreams are unreal, his satisfaction unfounded and his movements ridiculous, but he cannot restrain them; he can give a coherent account of his condition when aroused and answer questions intelligently. The sensation of pain is lessened or entirely absent, and the sense of touch is less acute than normally. Later the dreams alternate with periods of complete unconsciousness, from which the patient can be aroused easily, and the symptoms eventually pass into tranquil sleep, from which he awakes refreshed, and, as a rule, without any feeling of depression or nausea. In the majority of cases the preliminary stage of exaltation is very short or entirely absent in Europeans, the first effects of the drug often being heaviness, drowsiness, noises in the ears and numbness of the extremities, which pass into deep sleep. According to Dixon the drug is much more exhilarating when inhaled than when swallowed, and this may account for some of the variations in its action. In some cases, acute mania and convulsive attacks have been developed, and among the natives of India catalepsy occasionally occurs.

In animals the effects of cannabis indica seem to resemble those in man and present the same marked variations; a stage of exaltation with increased movement is sometimes present and is followed by no constipation. Pleasant dreams when inhaled. Pulse up. Cannabinol + glucuronic acid in urine. May lead to mania or dementia in West. Not nutritional disturbances as opium. Tolerance. Big doses not fatal. Preparations vary

Used in sleepless from nervous exhaustion + pain (when opium contraindic.) 50% sleep

depression, lassitude and sleep. The reflex excitability is first increased and then diminished in frogs. Vomiting is often induced in dogs and cats, but cannabis indica differs from opium in producing no disturbance of the digestion and no constipation. The heart is generally accelerated in man when the drug is inhaled; the intravenous injection in animals slows the pulse partly through inhibitory stimulation and partly through direct action on the heart muscle. This action on the heart is stated by Dixon to be the cause of death after poisonous quantities, for he found the respiration persist for some seconds after standstill of the heart. The pupil is generally somewhat dilated. Polyuria is stated to occur in dogs in which cannabinol appears to be excreted by the kidneys in combination with glycuronic acid (Fränkel).

Death from acute poisoning is extremely rare, and recovery has occurred after enormous doses. The continued abuse of hashish in the East sometimes leads to mania and dementia, but does not cause the same disturbance of nutrition as opium, and the habitual use of small quantities, which is almost universal in some Eastern peoples, does not seem detrimental to them, although among Europeans it might possibly be as fatal as that of morphine. Some tolerance is rapidly acquired.

PREPARATIONS.

Cannabis Indica (U. S., P., B. P.), Indian hemp, the flowering tops of the female plant of Cannabis sativa (hemp), grown in the East Indies.

Extractum Cannabis Indicæ (U. S. P., B. P.), 0.02–0.06 G. (¼–1 gr.).

Fluidextractum Cannabis Indicæ (U. S. P.), 0.1–0.3 c.c. (2–5 mins.).

TINCTURA CANNABIS INDICÆ (U. S. P., B. P.), 1–2 c.c. (15–30 mins.).

The preparations vary extremely in strength and many are entirely inert, especially when they have been kept some time. The unofficial preparations, such as "cannabin tannate," cannabinon, etc., seem to be no more reliable than the pharmacopœial ones, and offer no advantages at all commensurate with their price. Physiologically tested preparations are provided by many firms.

Therapeutic Uses.—Cannabis indica is used as a hypnotic in cases of sleeplessness from nervous exhaustion and, less often, from pain. It is not nearly so reliable as opium, and in fact produces sleep in only about 50 per cent. of the cases, according to some authors. On the other hand, it does not disturb the digestion and produces no subsequent nausea and depression, and may therefore be employed in some cases in which opium is contraindicated. It is of use in some cases of migraine, and has been prescribed as a substitute for opium in mental diseases.

Lactucarium (U. S. P.), the dried juice of Lactuca virosa, the common lettuce, is reputed to have some hypnotic properties. It contains neutral bitter substances, *lactucin* and *lactucon*, and it has been stated recently that traces of hyoscyamine and atropine are also present. In any case its action is so feeble that half an ounce has been administered to a dog without effect, and it seems quite unnecessary to include it in the pharmacopœia.

Apomorph. – a morph. anhydride. Preserves stim. action – loses depress. of [illegible] vomiting centre ($\frac{1}{12}$–$\frac{1}{6}$ gr) – 10–15 min. No depression unless large dose. Attendant symptoms (emesis, sweat, salivation, mucous, tears, weakness) these even if dose too small for emesis (or beginning action)

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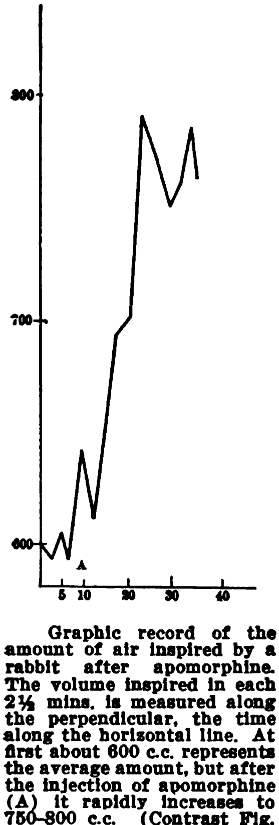
VII. APOMORPHINE.

When morphine is acted on by acids and by some other dehydrating agents, it loses a molecule of water, and a new alkaloid is formed, *Apomorphine* ($C_{17}H_{17}NO_2$).

Through this change the action of the original alkaloid is considerably modified; apomorphine preserves the stimulant, but loses to a great degree the depressant action of morphine on the central nervous system. This stimulant action extends over the whole central nervous system in animals, but is most developed in the "vomiting centre" of the medulla oblongata.

FIG. 20.



Graphic record of the amount of air inspired by a rabbit after apomorphine. The volume inspired in each 2½ mins. is measured along the perpendicular, the time along the horizontal line. At first about 600 c.c. represents the average amount, but after the injection of apomorphine (A) it rapidly increases to 750–800 c.c. (Contrast Fig. 18, p. 218.)

Symptoms.—In man apomorphine in doses of 5–10 mg. ($\frac{1}{12}$–$\frac{1}{6}$ gr.) induces within ten to fifteen minutes nausea and vomiting, accompanied by the usual attendant phenomena, but with no symptoms which cannot be directly included in these. Very often the nausea passes off immediately after the evacuation of the stomach, but when larger quantities have been administered, repeated vomiting and retching may occur. Occasionally depression and sleep follow the emesis after even small doses.

The attendant symptoms are profuse salivation, increased secretion of the mucous glands of the nose, throat and bronchial passages, tears and a cold perspiration. A feeling of depression and muscular weakness and acceleration of the pulse are also well-known symptoms accompanying nausea and vomiting, and are present after apomorphine. These are all to be regarded as sequelæ of the emetic action, however, and not as due to the direct action of the drug on the glands and other organs. In a few instances the depression and weakness have passed into alarming collapse, but no actual fatality is recorded from the use of apomorphine.

Very small doses of apomorphine may induce the secondary symptoms without actual vomiting. Thus the saliva, perspiration, tears

Animals - gt excitement - accel. of resp - tetanic convulsions -
In emesis no local action on stomach
Excreted in stomach, resp - decomposed to
Apocodeine paralyzes sympath. gang as nicotine
removes normal inhib of bowel movement = purgation

and other secretions may be augmented by quantities which are too small to act as emetics, though there is no question that these are due to the commencing emetic action.

In dogs and cats, small quantities elicit the same effects as in man, but larger doses are followed by symptoms of general nervous stimulation. In the herbivora, which are incapable of vomiting, these symptoms follow the injection of comparatively small quantities and are much more marked. The rabbit, for example, becomes restless and easily alarmed; it moves about, climbs up the walls of its cage and gnaws anything it can reach. Circus movements are developed very often, especially in the dog, the animal running unceasingly in a circle and striking against obstacles in its path, apparently unconscious of all its surroundings and overcome by the impulse to continual movement. The respiration is very much accelerated (Fig. 20). After very large quantities the movements become less coördinated, and eventually tetanic convulsions set in, during which the respiration ceases, while the heart continues to beat for some time afterward.

Apomorphine induces vomiting through changes in the medulla oblongata and not by irritation of the stomach. This is shown by the fact that it acts much more quickly and in smaller doses when it is injected hypodermically than when it is swallowed, and also by the fact that if the medulla be brushed with apomorphine solution, vomiting follows immediately. It is even disputed whether apomorphine has any effect on the gastric movements at all, for Batelli states that the stomach remains quite passive during vomiting, while Schütz found it undergoing antiperistaltic movements towards the cardiac orifice. In any case the movements of the stomach play an unimportant part in the evacuation of its contents by apomorphine, and all the phenomena in man are to be ascribed to medullary action.

Apomorphine is said to have some anæsthetic effects on the cornea when a solution is dropped upon it. It causes cloudiness and consequent dimness of sight, however, and has not been used practically for this purpose. Apomorphine is not excreted into the stomach like morphine, nor has it been found in the mucous membranes of the air passages, and it is possible that it is decomposed in the tissues.

The symptoms induced by apomorphine resemble in some degree those following morphine in many animals, for here too the first symptom is vomiting accompanied by signs of excitement, which are, however, generally attended by those of depression of some parts of the central nervous system. The similarity between the effects of apomorphine and of morphine on the cat, for example, is particularly striking. In man, however, the effects are very different, for apomorphine seems to have lost all the depressant action of the parent body, although here again it must be remembered that morphine occasionally causes vomiting, so that apomorphine does not depart so far from the type of the opium alkaloids as would at first sight appear.

In the frog, apomorphine causes a transient stimulation of the central nervous system, followed by depression and paralysis.

Apocodeine is formed from codeine in the same way as apomorphine from morphine, but it differs entirely from apomorphine in its action and resembles nicotine in paralyzing the sympathetic ganglia. It causes purgation when injected hypodermically, apparently from removing the normal inhibi-

$\frac{1}{20}$ - $\frac{1}{10}$ gr - Ap. Used by hypo (vomit) or by mouth for expectoration.
Other emetics mostly by mouth: - ipecacuanha. tartar emetic. amm. carbonate.
sulphates of Zn. Cu. Alum. Note. Emesis dangerous in corrosive poisoning when
walls weak.

Narcosis may have depressed vomiting centre. Stomach tube preferable.

tion of the bowel movements (Dixon). If codeine be heated with hydrochloric acid (B. P.), apomorphine is formed, and not apocodeine.

Infl. resp. passages ↑ mucous secretion (small doses). Better ipec.. antimony etc
as these less depressant. Contraind. where high [illegible] dangerous (circ. cond., pregnancy, gastric ulcer, hernia)

PREPARATIONS.

✓ APOMORPHINÆ HYDROCHLORIDUM (U. S. P., B. P.), 3–6 mg. ($\frac{1}{20}$–$\frac{1}{10}$ gr.).
INJECTIO APOMORPHINÆ HYPODERMICA (B. P.), 1 per cent., 5–10 mins.

Apomorphine hydrochlorate is a grayish-white crystalline substance, very soluble in water and turning dark green or even black, especially when kept long in solution. This change in color does not appear to impair its activity appreciably. The doses given above are those for hypodermic use to induce vomiting. The same quantity may be given by the mouth as an expectorant.

Therapeutic Uses.—Apomorphine is used chiefly as an emetic, and for some purposes presents several advantages over the older drugs employed with this object, inasmuch as it acts more promptly and can be administered by the hypodermic needle, while the other emetics have to be given by the mouth, which is a serious drawback in cases of poisoning. The more important of these older drugs are ipecacuanha, tartar emetic (antimony), ammonium carbonate, the sulphates of copper and zinc and alum.

Vomiting is not now such an important method of treatment as it was formerly, and the emetics are less frequently employed to evacuate the stomach than other less heroic measures, such as the passage of the stomach tube. Emesis may be indicated in poisoning, and here apomorphine is especially useful. But in the great majority of cases a better method of treatment is repeated washing of the stomach by means of the stomach tube, for in narcotic poisoning apomorphine not infrequently fails to act, owing to the depression of the vomiting centre, and in corrosive poisoning a certain amount of danger attends its use, as the pressure on the walls of the stomach exerted by the contraction of the diaphragm and abdominal muscles may lead to the rupture of the weakened walls of the organ. In irritant poisoning, on the other hand, the reflex vomiting set up is generally sufficient to empty the stomach, and the indications are rather to allay the gastric irritation than to increase it by causing violent movements of the abdominal walls by apomorphine. Emetics, such as apomorphine, have been used occasionally to cause pressure on other abdominal organs, *e. g.*, on the gall-bladder in order to dislodge a calculus or plug of mucus in the ductus choledochus, but this treatment is not to be advised, owing to the risk of rupture of the gall-bladder. Occasionally emetics are used, especially in children, to expel bodies from the air passages, as violent movements of expiration are produced during emesis. Apomorphine is comparatively rarely used for this purpose, however. In cases of choking due to foreign bodies lying in the pharynx, vomiting is often beneficial, but the emetics act too slowly to be of benefit here.

A second use of emetics is in inflammatory conditions of the respiratory passages; the object here is to induce an increased secretion without producing emesis, and very small quantities are therefore used. The special condition in which this class of remedies is of service is bronchial irritation with a sticky mucous secretion which causes cough, but can only be expectorated with difficulty. The indications are for a mild and prolonged action such as can be induced by small doses of ipecacuanha, antimony and similar bodies, rather than for the more transient effects of apomorphine, but the latter has been advised by some authorities.[1]

Emesis is contraindicated in all conditions in which a sudden rise of blood-pressure may be dangerous, as in atheroma, fatty heart or aneurysm, and where there is any danger of rupture of the abdominal walls or organs as in hernia, advanced pregnancy (especially if there be any tendency to abortion), gastric ulcer and impacted gall-stone.

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VIII. PRUSSIC ACID.

Prussic or hydrocyanic acid differs entirely from the other acids in its pharmacological action, and has therefore to be described apart from them.

The pure acid is scarcely ever seen save in the chemical laboratory, and is an extremely dangerous body to handle, as it is very volatile and when inhaled may produce death within a few seconds. It is generally met with in a very dilute solution, which is formed by the decomposition of one of its salts.

In nature, prussic acid occurs in the secretion of some of the myriapoda, and in the decomposition products of a few glucosides, of which *Amygdalin* is the best known. Amygdalin is in itself practically inactive, but may be decomposed by dilute acids or by a ferment, emulsin, which is generally found associated with it in plants. The products of its decomposition are prussic acid, benzaldehyde and glucose (see p. 65).

Both amygdalin and emulsin occur in the bitter almond and in the kernels of a number of fruits, such as the apple, cherry, prune, plum and apricot. In smaller quantities they have been found in the bark and leaves of several of these trees and in the laurel (Prunus laurocerasus). In the sweet almond emulsin occurs, but no amygdalin. When bitter almonds are rubbed into a paste with water, prussic acid is formed by the action of the ferment on amygdalin, and very large quantities of such a paste may give rise to unpleasant symptoms, especially in children. A more dangerous substance is the oil of bitter almonds, which consists of benzaldehyde and prussic acid in a loose combination and in very varying proportions. Several liqueurs are distilled from kernels and fruits containing amygdalin, and therefore possess a variable percentage of prussic acid. The best known of these are Kirschwasser and Maraschino. Laurel water and the preparations of Virginian cherry bark contain benzaldehyde and prussic acid, although these are in too small quantity to have any poisonous action.

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[1] Apomorphine is occasionally mentioned as a hypnotic in doses of $\frac{1}{30}$ gr.

Prussic acid and its salts have practically the same action, although none of the latter are so poisonous as the free acid. Cyanogen, $(CN)_2$, also resembles prussic acid in its effects, but is not so active.

The ferrocyanides and other double cyanides are in most cases harmless but other compounds, from which prussic acid is formed in the organism, are poisonous. The organic combinations containing the $-CN$ radicle form two series, the *Nitriles,* in which the nitrogen is trivalent (*e. g.,* $CH_3-C\equiv N$), and the *Isonitriles,* or *Carbylamines,* in which the alkyl is attached to the nitrogen (*e. g.,* $CH_3-N\equiv C$). These compounds are all much less poisonous than prussic acid, and the nitriles are said to differ from it in their effects, inasmuch as the chief symptoms caused by them arise from gastro-intestinal irritation. The isonitriles are more poisonous than the nitriles and resemble the acid more closely in their action. Both nitriles and isonitriles give rise to the formation of prussic acid in the tissues.

Symptoms and Action.—Prussic acid first stimulates and then paralyzes the central nervous system in mammals, but it acts on so many forms of living matter that it merits the designation of a general protoplasm poison. The fatal dose in man is believed to be about 0.05–0.08 G. (1–1½ gr.) of the pure acid, certainly a much larger quantity than is fatal in cases of poisoning with some of the alkaloids and glucosides. Prussic acid acts much more rapidly than these, however, and has thus gained its reputation of being the most dangerous of poisons.

After very large doses in mammals, there may be practically no symptoms; the animal falls to the ground with a slight convulsive movement or a scream, and death follows in a few seconds from simultaneous arrest of the heart and respiration.

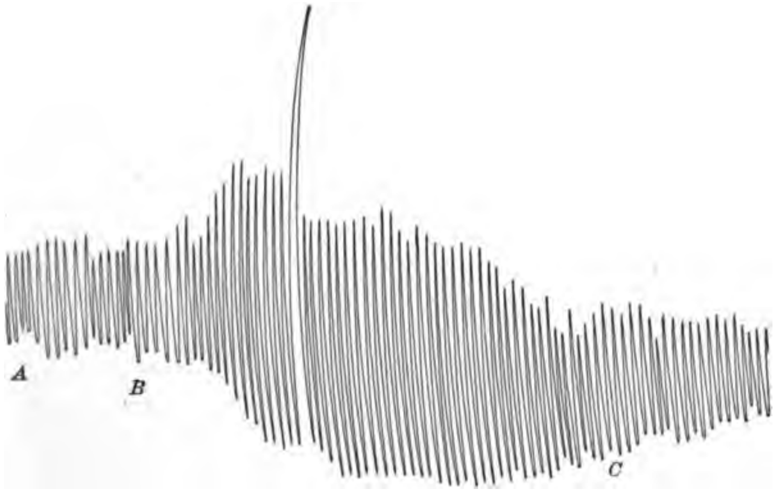
In smaller quantities prussic acid has a bitter, acrid, burning taste, which is accompanied by salivation, and is followed by numbness in the mouth and throat. A sensation of warmth in the stomach is followed by nausea and vomiting, confusion and headache, dyspnœa, slow pulse and general muscular weakness. The pupils are widely dilated and the eyeballs protrude, as generally occurs in asphyxia. Unconsciousness follows, and then violent convulsions, which pass into paralysis with involuntary evacuation of the contents of the bladder and bowels, the respiration becomes extremely slow and eventually ceases, while the heart continues to beat for some time afterwards.

In frogs, no convulsions occur, the symptoms pointing to a paralysis of the central nervous system without preliminary stimulation, except in that the respiration is somewhat quick and dyspnœic.

In mammals the **Central Nervous System** is first stimulated and then paralyzed, but the action seems to be developed more fully in the medulla oblongata and lower parts of the brain than in the cerebral cortex, for the convulsions resemble those produced by stimulation of the hind-brain, although the subsequent paralysis seems to include all parts of the central axis.

The peripheral **Muscles** and the **Nerves** are weakened and eventually paralyzed when suspended in an atmosphere of the gas, but they are not affected in poisoning; the nerves are more readily poisoned than the muscles. When prussic acid in solution is applied locally to the **Skin**, it produces numbness and partial loss of sensation, but this does not follow in general poisoning. The anæsthetic action is well seen on brushing the leg of a frog with a weak solution, for no reflex can be elicited from subsequent irritation of the limb, although it is moved on irritation of other parts of the body, which shows that the motor nerves and the spinal cord are still intact.

FIG. 21.



Tracing of the movements of the diaphragm (respiration) of the rabbit under a large but not fatal dose of cyanide of potash injected intravenously. *A–B*, normal respiration. At *B* 1 mg. injected; the respiratory movements are much larger. At *C* recovery. Note the short duration of the stimulation.

The **Respiration** is rendered quicker and deeper by the injection or inhalation of small quantities of prussic acid. During the convulsions it is, of course, irregular, and afterwards generally becomes extremely slow and deep and then ceases. After very large quantities it may cease within a few seconds. These changes are produced by primary stimulation and subsequent paralysis of the medullary centre.

The **Circulation** is altered mainly through the action on the central nervous system, although prussic acid also acts directly on the heart. The stimulation of the inhibitory centre generally slows the pulse, but this is accompanied by a very considerable rise in blood-pressure from increased activity of the vaso-constrictor centres. This central stimulation later passes into paralysis and the blood-pressure falls, from the depression of the vasomotor centres, but the heart does not generally regain its normal rhythm, because although the inhibitory stimulation has passed off, the cardiac muscle is now directly affected, and its movements therefore remain somewhat slow. During the convulsions the arterial pressure rises again, but afterwards the progressive weakening of the heart leads to a slow and imperfect circulation. In the frog's heart prussic acid causes slowing and standstill long before the peripheral nerves and muscles are affected.

Nutrition.—Besides its specific action on the central nervous system, prussic acid exercises a depressant action on protoplasm in general, and may therefore be called a general protoplasm poison, although some of the bacteria are but little affected by it. Both plants and animals are retarded in their movements and in their nutritive processes by its presence, although they may recover and show no subsequent deterioration provided the poison acts only during a short time and in sufficient dilution. For example, the development of seeds is hindered by the presence of prussic acid, but proceeds when it is withdrawn; yeast cells cease their activity, and the insectivorous plant Drosera no longer moves its tentacles in the presence of cyanides or prussic acid (Darwin). This action in plants is probably due to the poison arresting the activity of the ferments and the respiration of the cells.

The effects of prussic acid on the mammalian tissues have been examined by Geppert in a long and careful research. He found that the oxygen absorbed by the tissues was much lessened by prussic acid, whereas it was to be expected that a convulsive poison, such as that under discussion, would cause an increased waste in the tissues and a corresponding rise in the oxygen used; yet during the most powerful convulsions after prussic acid, the absorption of oxygen is often distinctly lower than in the normal resting animal. After some time the consumption of oxygen again increases, although it does not regain the normal standard unless complete recovery occurs; the carbonic acid actually formed by the tissues falls, owing to the lessened oxidation, and Geppert proceeded to prove that the imperfect oxidation is due to the fact that the tissues are unable to absorb the oxygen brought to them by the blood cells; that, in fact, a change occurs in the protoplasm, which retards the normal respiration of the cell. In consequence of this, the oxyhæmoglobin of the blood is not reduced in the capillaries, so that the venous blood has the same bright-red color as the arterial. Prussic acid seems to be rapidly changed to other products in the tissues, however, provided a lethal dose has not been given, and as this process goes on the protoplasm recovers its oxygen-absorbing power, the expired air becomes less rich in oxygen and richer in carbonic acid, and the venous blood assumes its ordinary dark color. The usual results of imperfect oxidation in the tissues are seen in an increase in the sugar and lactic acid in the blood.

Imperfect oxidation is also the chief cause of the augmented nitrogen, urea and unoxidized sulphur of the urine. But some other changes in the urine do not seem to be adequately explained by this factor and may arise from some hitherto unrecognized action of the poison (Richards and Wallace).

The changes in the central nervous system are produced by smaller quantities and somewhat more rapidly than those in the metabolism, and they also last longer. The dilatation of the blood vessels from the depression of the vaso-constrictor centre may probably coöperate with the lessened absorption of oxygen to produce the bright red color of the venous blood.

The diminution in the oxygen absorption by the tissues is apparently due to the action of the intracellular ferments being arrested by prussic acid, and there thus seems to be an entire correspondence between the changes produced in the metabolism of plants and animals by prussic acid.

Prussic acid is changed to sulphocyanides in the tissues, and is partly excreted in the urine in this form, while part of it undergoes further and unknown changes. This combination of prussic acid and sulphur bodies, such as the proteins, seem to arise by simple chemical processes, without the intervention of living protoplasm being necessary.

In the living body prussic acid does not form any combination with the hæmoglobin of the red blood cells, but in the drawn blood it appears to form cyanhæmoglobin, a loose combination which differs slightly from hæmoglobin in its spectrum and is reduced with greater difficulty, so that the blood retains its red color longer. If normal blood be brought in contact with a solution of peroxide of hydrogen, it effervesces, owing to the liberation of oxygen by the peroxidase ferment, and the peroxide being all decomposed in this way, the oxyhæmoglobin remains unchanged; if, however, prussic acid be present, no effervescence occurs, and the hæmoglobin is at once changed to methæmoglobin from the oxidizing action of the peroxide, which is no longer dissipated. In cases of poisoning with cyanides, the dependent parts of the body often present a bright red color instead of the usual post-mortem lividity, and this seems due to the cyanhæmoglobin retaining its red color, while ordinary oxyhæmoglobin is reduced.

PREPARATIONS.

Acidum Hydrocyanicum Dilutum (U. S. P., B. P.), a two per cent. solution formed from potassium ferrocyanide or silver cyanide. It is a colorless fluid with a characteristic smell and taste, and ought not to be kept long, as it is liable to decomposition; much of that actually used in medicine is partially decomposed and therefore under two per cent. in strength. Dose, 0.1–0.5 c.c. (2–8 mins.).

A number of other preparations contain prussic acid, generally in very variable quantity. Thus in the U. S. P. the preparations of bitter almonds, except the expressed oil, contain it, and the volatile oil is, in fact, dangerous owing to the large proportion of prussic acid sometimes present. Another series of preparations containing it, though only in minute quantities, is that of the bark of the wild cherry, Prunus Virginiana. In the British Pharmacopœia the bitter almond, Virginian cherry and the cherry-laurel water contain it, but only in harmless quantities. It is also present in the tincture of chloroform and morphine, B. P.

Therapeutic Uses.—The uses of prussic acid at the present day are very few. Externally it is applied to itching surfaces to cause numbing and insensibility of the sensory nerve terminations, but the members of the cocaine group are much more efficient. It is also used internally in vomiting, especially in that occurring in pregnancy, but here also orthoform and other local anæsthetics should be preferred. It was formerly used extensively as a sedative in cough, but was generally prescribed along with opium or other narcotics, and it seems unlikely that the hydrocyanic acid had any effect.

In **Poisoning** with prussic acid or the cyanides, the treatment is that of poisoning in general—thorough evacuation of the stomach, warmth and general measures against collapse. Artificial respiration should be resorted to when necessary, as a cyanide is comparatively quickly rendered inactive, and the recovery is rapid when it once sets in. The intravenous injection of sodium sulphide and hyposulphite has been advised on the theory that the comparatively harmless sulphocyanide would be formed, and animals seem to be able to survive an otherwise lethal dose when this is done. This, however, like other proposed antidotes, is not generally applicable in an emergency, and if prussic acid is not fatal within a few minutes, recovery may be looked for without any treatment. But in many cases life is extinct before medical aid can be called.

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IX. CAFFEINE.

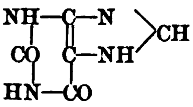
In a number of plants used in different parts of the world to form beverages and condiments, there are found the xanthine compounds, *Caffeine, Theobromine* and *Theophylline* (*Theocine*), which have been employed in therapeutics of late years, and have, therefore, acquired a double importance as drugs and as articles of diet. The wide-

Widespread use. [illegible]. No pleasurable effects as alcohol etc. Brighten intellect, increases capacity for physical + mental work.
Action on cns.. All on kidneys. muscle & heart.

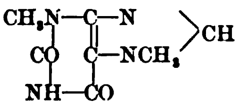
spread use of preparations of these by uncivilized peoples is a curious and unexplained fact, especially as they possess neither peculiar taste nor odor to guide in the selection of the plants in which they exist. Besides, caffeine and its allies in moderate quantities induce no marked symptoms, such as follow the use of alcohol, opium or hashish and explain their use among widely separated peoples. On the contrary, the only effects to be observed are a brightening of the intellectual faculties and an increased capacity for mental and physical work. Coffee, the use of which is derived from the Arabians, is the berry of Coffea Arabica and contains caffeine; tea, the leaves of Thea Chinensis, contains caffeine along with theophylline. Cacao, cocoa or chocolate is derived from the seeds of Theobroma cacao, a tree indigenous in Brazil and Central America, and contains theobromine. In central Africa, the Cola or Kola nut (Sterculia acuminata) is used by the natives, and contains caffeine with small quantities of theobromine. In Brazil, Guarana paste is formed from the seeds of Paullinia sorbilis, and contains caffeine and theobromine, while in the Argentine Republic, Yerba Mate or Paraguay tea (Ilex Paraguayensis) is used to form a beverage which contains a very small quantity of caffeine. Another species of Ilex is met with in Virginia and Carolina under the name of Apalache tea or Youpon, and also contains caffeine.

These three principles, caffeine, theobromine and theophylline, are purine derivatives closely related to the xanthine bodies found in the urine and tissues of the animals. The members most closely approaching the vegetable forms are xanthine, paraxanthine and heteroxanthine; the last is a monomethylxanthine, while paraxanthine is a dimethylxanthine isomeric with theobromine and theophylline, and caffeine is trimethylxanthine. The structural formulæ may serve to indicate more clearly the close relationship of these bodies.

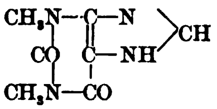
Xanthine.



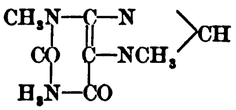
Theobromine.



Theophylline.



Caffeine.



Action.—These all resemble each other in most points of their pharmacological action, although caffeine acts on the central nervous system as well as on the kidneys, muscle and heart, while theobromine has comparatively little effect except on the last three.

Central Nervous System.—In mammals the injection of large quantities of caffeine is followed by symptoms closely resembling those induced by strychnine. The reflex irritability is remarkably increased, the lightest touch being followed by powerful contraction of almost all the muscles of the body. After a time these contractions occur

[illegible] diminished · Rapid ideas = confusion in large doses. Often used [illegible]
restlessness · Acuteness of sensations as touch. Tolerance · Occasionally
headache, tremor, palpitations & quickened rate · Medulla stim · [illegible]
[illegible] slower but direct action = strong beat
[illegible] intra-cranial

without any apparent stimulus, and culminate in tonic convulsions which last for several seconds. During these, the respiration ceases because the respiratory muscles are involved in the spasm, and occasionally it fails to be reinstated when the convulsions pass off. In other instances the spasms become weaker and occur at longer intervals; the respiration diminishes in frequency and depth and eventually ceases.

In man smaller quantities of caffeine stimulate the central nervous system, in particular that part associated with the psychical functions. The ideas become clearer, thought flows more easily and rapidly, and fatigue and drowsiness disappear. Not infrequently, however, connected thought is rendered more difficult, for impressions follow each other so rapidly that the attention is distracted, and it requires more and more effort to limit it to a single object. If the quantity ingested is small, however, the results are of distinct benefit in intellectual work. The capacity for physical exertion is also augmented, as has been demonstrated repeatedly by soldiers on the march, and more recently by more exact experiments with the ergograph. The stimulation of the higher nervous centres is often evidenced by the insomnia and restlessness which in many people follow indulgence in coffee or tea late at night. Kraepelin has investigated the effects of caffeine from the psychological point of view, and finds that both tea and coffee facilitate the reception of sensory impressions and also the association of ideas, especially in fatigue, while the transformation of intellectual conceptions into actual movements is retarded. This he regards as due to stimulation of the highest or controlling functions of the brain, caffeine acting on the same parts as are first affected by alcohol and the methane derivatives, but altering them in the opposite direction. The effects of caffeine on the acuteness of the senses has been demonstrated by the greater accuracy of touch under its influence.

Large quantities of caffeine often cause headache and some confusion, and in rare cases of special susceptibility a mild form of delirium may be elicited, or noises in the ears and flashes of light may indicate derangement of the special senses. The pulse is quickened, and occasionally palpitation and uneasiness in the region of the heart are complained of. Convulsive movements of the muscles of the hand and tremor in different parts of the body have also been recorded in some cases. These effects are induced only with difficulty in habitual drinkers of tea or coffee, so that the continued administration of small quantities of caffeine evidently gives rise to tolerance.

The symptoms induced by caffeine in the lower mammals are due for the most part to its acting on the spinal cord in the same way as strychnine, though small doses may act on the brain, for they often elicit restlessness and timidity without any marked change in the reflex excitability. The centres in the medulla oblongata are also involved in the effects, as is indicated by a rise in the blood-pressure from stimulation of the vasomotor centre, acceleration of the breathing, and occasionally some slowness of the pulse from action on the respiratory

Caffeine's action psychical. Strychnine's on vitals & reflex functions. Theophylline on cns, theobromine not. Injection into muscle = rigidity locally – rigor mortis. Small quantities, irritability increased, + capacity for work + fatigue delayed.

and pneumogastric centres. The intracranial blood vessels are said to be dilated.

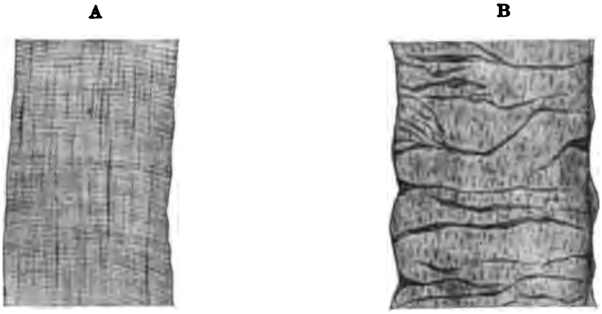
Frogs show no nervous symptoms that cannot be ascribed to action on the spinal cord, and in some species these are elicited with considerable difficulty owing to the muscular action described below.

On comparing the effects of caffeine and strychnine on the central nervous system it will be found that while there is a general similarity in their action, the latter causes more marked stimulation of the lower divisions and has less action on the cerebrum in mammals and man. They both produce a general increase in the activity of nerve cells, but caffeine acts more on the psychical, strychnine more on the vital and reflex functions.

Theophylline resembles caffeine in its action on the central nervous system, while theobromine induces few or no symptoms of stimulation. The monomethyl-xanthines and xanthine itself stimulate the central nervous system in the frog (Schmiedeberg).

The **Muscular** action of caffeine is best seen in the Rana temporaria (grass frog), although it is also induced in other species of frogs, and some rigidity may be elicited in mammals by very large doses. When a few drops of caffeine are injected into the leg of a frog there follows a peculiar stiffness and hardness in the muscles around the point of injection, which slowly spreads to other parts of the body and induces the appearance of rigor mortis. The same effect is observed when teased muscle fibres are subjected to a caffeine solution under a high-power microscope. The fibres contract, become white and opaque, and look stiff and inflexible; the transverse striæ disappear, while the longitudinal become more easily visible (Fig. 22). This appearance is due to the death and rigor mortis of the fibres. Fürth states that the myogen of muscle is formed into myogenfibrin and coagulated by the addition of caffeine to its solutions outside the body, so that the rigor induced by caffeine seems due to a comparatively simple reaction between the poison and the proteins of the muscle fibre.

FIG. 22.



A muscular fibre of the frog (highly magnified). A, normal; B, after the application of caffeine solution. The coarse striæ in B are the folds of the sarcolemma.

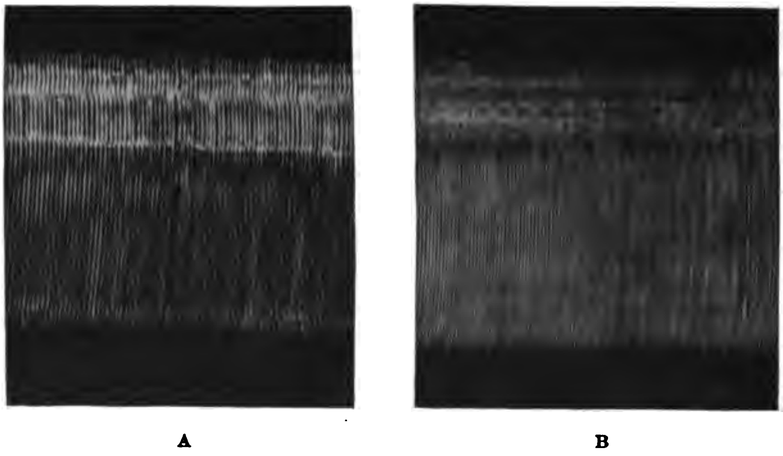
In small quantities caffeine increases the irritability of muscle as

Va. Mus- rates abs Incr ex. Large quantities both decrease [illegible] rigor.
increased irritability of musculature but more than of X!
Resp center irritable — so good in morph. Alcohol etc poisoning

well as its absolute strength and extensibility, that is, the muscle contracts on a weaker stimulus and against a greater load than it does normally. The amount of work done before fatigue sets in is also increased, unless when large quantities are applied, when the capacity for work is lessened; and with the first appearance of rigor it ceases to react to stimuli altogether. Sobieranski has recently shown that in ordinary doses caffeine increases the work done by the human muscles when they are stimulated by electric shocks. The universally recognized effect of tea and coffee in increasing the capability for physical work and in relieving fatigue has generally been regarded as due to changes in the nerve cells, but according to Kraepelin and others is really of peripheral origin and explained by the direct action on the muscle. While the action of theobromine on the central nervous system is much less marked than that of caffeine, muscle enters into rigor after the former more readily, and xanthine exceeds even theobromine in its power to produce this change.

The action of caffeine on the **Circulation** is exerted in two directions, on the vasomotor centre in the medulla and on the heart itself. Along with the rest of the central nervous system, the vasomotor area undergoes stimulation and the smaller arteries are therefore contracted, causing a rise in the arterial pressure.

FIG. 23.



Tracing of the ventricle of the dog's heart: A, normal; B, after caffeine. The lever moves upwards during systole, downwards during diastole. The only alteration caused by caffeine is acceleration. The slightly larger excursion in diastole in B is mechanical. (Contrast tracings under digitalis.)

In the frog's heart caffeine in very small quantities is found to increase the absolute strength, that is, the heart contracts against a greater aortic pressure than it would normally, and at the same time the amount of blood expelled by each beat is slightly increased. The rhythm is generally somewhat accelerated by small doses, but this effect is often of very short duration. On the absorption of larger quantities, the heart first becomes slower and its volume smaller, Theobr. & Xanthin have little effect on v.m., but act on muscle.

then the apex ceases to relax with the rest of the ventricle and remains white and contracted, and eventually the whole heart passes into a condition of rigor exactly resembling that seen in the skeletal muscles.

When moderate quantities of caffeine are injected intravenously in mammals, the heart is accelerated, without any marked change in the extent of systole or diastole. The increased rate is independent of any action on the regulatory mechanism of the heart, for it is seen in hearts in which the accelerans has been cut and the inhibitory apparatus paralyzed by atropine. It is probably due to direct action on the heart muscle, for, as has been stated, an analogous increase in irritability occurs in voluntary muscle. The increased irritability of the cardiac muscle also accounts for the fact that stimulation of the vagus is followed by less slowing of the heart after caffeine than before its administration. In man the heart rhythm is often found slower after caffeine, and this appears to be due to stimulation of the inhibitory centre in the medulla oblongata, the increased inhibition proving more than sufficient to counterbalance the acceleration which would arise from the direct action of the caffeine on the heart muscle. And it seems unlikely that sufficient caffeine ever reaches the heart in man to cause the very rapid beat which is elicited in experiments in animals. Similarly, the weakness and irregularity of the heart which follows the intravenous injection of large quantities of caffeine in animals, does not occur in man. Sometimes palpitation is complained of from excessive coffee or tea drinking, but this may rather be ascribed to the increased activity of the inhibitory apparatus than to the stimulation of the cardiac muscle, though this cannot be excluded altogether. The increased rate of the heart in animals is not always accompanied by an increase in the amount of blood expelled in a unit of time (Bock), although this is often the case. Apparently the contractions of the ventricle follow each other so rapidly that the time is often insufficient for the inflow of the usual amount of blood. The increase in the blood-pressure under caffeine is therefore to be ascribed for the most part to the action on the vasomotor centre, although not infrequently this is supplemented by an increased efficiency of the heart. Theobromine and xanthine possessing but little action in the vasomotor centre, scarcely raise the blood-pressure although they have the same effect on the heart as caffeine. Some increase in the flow through the coronary vessels is sometimes seen under caffeine and more especially under theobromine, but it is not determined whether this is due to a direct action on these vessels or to the increased activity of the heart.

The **Respiration** is quickened and strengthened by caffeine, owing to a stimulant action on the medullary centre. This is seen in the improvement of the respiration in cases of dangerous poisoning with alcohol, opium and other drugs which prove fatal by depressing the centre, but is much less marked in normal animals.

The **Temperature** has been found to be raised by caffeine through its

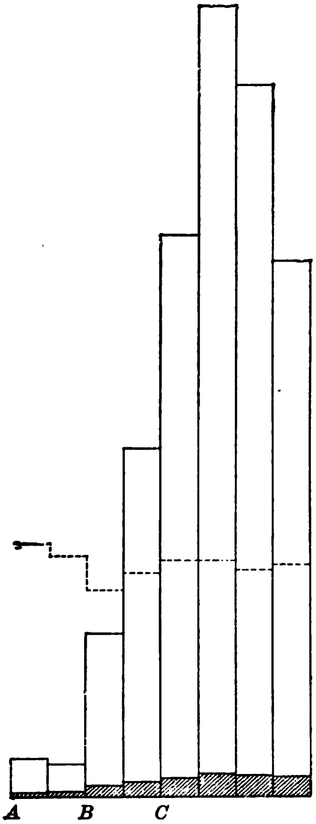
Theobr + theophylline irritate stomach. Not so caffeine

action on the nervous centres and perhaps on the muscles. The increase is, however, comparatively insignificant (0.5–1° C.) and is seen only in cases in which an almost poisonous dose has been used.

The **Alimentary Tract** is not affected by caffeine, but after theobromine discomfort and loss of appetite are sometimes complained of, probably owing to changes in the gastric mucous membrane. These are much more marked after even small doses of theophylline, and small hæmorrhages and erosions have been found in the stomach, both in man and animals (Allard).

Kidney.—The most important property of caffeine from a therapeutic point of view is its power of increasing the secretion of urine. It is an everyday experience that strong coffee or tea increases the urine to a much greater extent than the same amount of water, and this has been shown to be due to the caffeine contained in these beverages. It is still disputed how caffeine causes diuresis, for while the most generally accepted view is that of Schroeder, that caffeine acts directly on the renal cells, some investigators hold that the increased urinary secretion is due to local changes in the renal circulation. As a general rule the vessels are dilated and the kidney volume is enlarged during caffeine diuresis, but this may be merely an accompaniment and not the cause of the increased activity. The experiments of Cullis indicate that in the frog, and presumably also in mammals, the diuresis is due to changes in the renal tubules, for it continues after the blood supply to the glomeruli is cut off. In any case the diuresis is due to changes within the organ, and is quite independent of the action of the drug in other parts of the body. These may in fact counteract the real action and prevent the diuresis, through stimulation of the vaso-constrictor centre, which retards the circulation in the kidney and lessens the amount of fluid reaching the renal cells

FIG. 24.



Caffeine diuresis in a rabbit. The amount of urine passed in ten minutes is represented by the height of the rectangles. The first of these, *A-B*, represent the normal secretion. At *B* a small dose, and at *C* a large dose of caffeine was injected intravenously, and the secretion is accordingly increased. The shaded part of the rectangles represents the amount of solids in the urine. It will be noted that these are increased but not to the same extent as the fluid. The dotted line represents the average height of the blood-pressure during each period of ten minutes. The animal had received a large dose of chloral to depress the vasomotor centre and the heart, and caffeine had, therefore, little or no effect on the height of the blood-pressure.

V-const: [illegible]
(as give diuresis theob n theophylline). Fluids more than solids. Of latter eg NaCl
Glycosuria not specific – merely carried out in fluid (1) In oedema dropsy
to replace fluid of blood normally from g.i. as thirst. Theob. no nervous n restlessness
lasts longer. Mostly excreted out urine as urea. no increase
of uric acid

(Schroeder). This inhibitory action of the vasomotor centre may be eliminated by such medullary depressants as chloral, under which the caffeine diuresis may be elicited with much greater certainty. Theobromine has a more constant effect on the kidney and causes even greater activity in that organ than caffeine, and this was explained by Schroeder as being due to its having little or no stimulant effect on the vaso-constrictor centre. Theophylline appears to increase the urine more than any other of the group, with the possible exception of paraxanthine.

In the caffeine diuresis the fluid part of the urine is increased chiefly, but the solids also undergo an augmentation, though not to the same extent. Among the solids the chief increase is seen in the sodium chloride, the nitrogenous constituents undergoing less alteration, although they also rise in amount; a small amount of sugar is often found in the urine, more especially if the food has contained large quantities of sugar-forming substances, but this glycosuria is probably due merely to the large quantities of fluid sweeping some of the sugar of the blood along with it, and does not indicate any dangerous alteration in the renal epithelium or in the metabolism.

The excretion of large quantities of fluid in the urine is, of course, accompanied by a diminution of the fluids of the blood, but the latter soon recuperates itself from the tissues. If there is any accumulation of liquid, such as œdema, it is drained into the blood to replace the fluid thrown out by the kidney, and caffeine may accordingly be used to remove œdema or dropsy in this way. If no such accumulation exists, the blood draws on the fluids of the intestine and stomach, and their withdrawal leads to the sensation of thirst. As a diuretic, caffeine is distinctly inferior to theobromine; in the first place because the diuresis is less certain and is often accompanied by nervous symptoms—sleeplessness and restlessness; and secondly because the increase in the secretion is smaller and lasts for a shorter time.

Excretion.—Caffeine is excreted in the urine to a very small extent as such. During its passage through the body it loses its methyl groups and first becomes dimethyl- and then monomethylxanthine. Eventually xanthine is formed and this probably breaks up into urea. In the urine are found small quantities of the unchanged drug, accompanied by larger quantities of dimethylxanthine and monomethylxanthine. After theobromine and theophylline some of the unchanged drug is found in the urine along with monomethylxanthine. The uric acid of the urine is not increased by any of these drugs.

The exact order in which the methyl groups are lost in the tissues appears to differ in different animals; in the dog all three isomeric dimethylxanthines are formed from caffeine and after large doses appear in the urine, although theophylline predominates, while in the rabbit and in man paraxanthine is formed in larger amounts. The monomethylxanthines are also excreted in different proportions in different animals, heteroxanthine prevailing in man and the rabbit.

Tolerance — [illegible] & tissues [illegible].
Give in sol. of salicylate of soda to dissolve - Caff. 1-5 gr.
Theob. - 2-8 gr. (Diuretine = theob. na. salic.)
Theocine or theophylline 3-5 gr

Tolerance.—A certain degree of tolerance is acquired from the prolonged use of coffee, tea or chocolate, as is shown by the absence of diuresis. Apparently the caffeine and its allies undergo more rapid destruction, but this does not explain the tolerance completely, for even after prolonged administration large quantities of these bodies may be obtained from the tissues, which must have ceased to react to them, as well as learning to destroy them more rapidly than normally.

Preparations.

/ **Caffeina** (U. S. P., B. P.), long, white, silky crystals, without odor, but possessing a bitter taste, but little soluble in cold water, more so in alcohol, still more so in boiling water. 0.05–0.3 G. (1–5 grs.). 1-5 gr

Caffeina Citrata (U. S. P.), *Caffeinæ Citras* (B. P.), a white powder, consisting of a weak chemical combination of citric acid and caffeine. It is decomposed by mixture with more than 3 parts of water. 0.1–0.5 G. (2–8 grs.). 2-8 gr

Caffeina Citrata Effervescens (U. S. P.), *Caffeinæ Citras Effervescens* (B. P.), a mixture of citrated caffeine with sodium bicarbonate, tartaric acid and sugar. On throwing the powder in water it effervesces, owing to the acids acting on the bicarbonate and liberating carbonic acid. This preparation contains only 2 per cent. of caffeine. Dose, 4 G. (60 grs.). 2% 4 G

Caffeine is best prescribed either in powder or in tablets. It may also be given in water with salicylate of soda, which aids its solution.

Theobromina (unofficial) is a crystalline powder even less soluble than caffeine, and is absorbed with difficulty when given alone. It is generally prescribed in doses of 0.5 G. (8 grs.) three times a day, but larger quantities may be given. Solutions of salicylate of soda dissolve it much more readily than pure water. 2-8 gr

Diuretine and *Agurine* are double salts of sodium-theobromine with the salicylate and acetate of sodium respectively and are much more soluble than theobromine. The dose is 0.5–1 G. three times a day, either in powder form or in solution.

Theocine, an artificial theophylline, is a white crystalline powder, slightly soluble in water. Dose, 0.2–0.3 G. (3–5 grs.) in powder or tablets.

Guarana (U. S. P.), a brown paste derived from the seeds of Paullinia sorbilis and containing caffeine and theobromine along with some tannic acid.

Numerous preparations of Kola nut are now put on the market, but the pure principles are preferable.

Therapeutic Uses.—The action of caffeine on the central nervous system has led to its employment in a number of different conditions. Thus, in nervous exhaustion it may be used to stimulate the brain, and in collapse its action on the vasomotor and respiratory centres has been found of value—the blood-pressure rises, the whole tone of the circulation is improved and the respiration becomes quicker and less shallow. In narcotic poisoning with failing respiration, caffeine may be used to stimulate the centre in place of strychnine or atropine; in opium poisoning more particularly, strong coffee has long been used, but caffeine might be substituted with advantage. Its stimulant action on the brain, and more especially on the respiration, renders it an antidote in dangerous cases of alcoholic poisoning also. Some forms of migraine and headache are relieved by caffeine, but in others it seems rather to intensify the pain; this action has been attributed

useful for resp. ctr. Morph. & alc. poisoni-
By dil. of cerebral vessels relieves some headaches. Its action for feeble heart
Also lessens its work if dropsy (+ digitalis) Doesn't lessen inflammatory effusion
or renal accumulation if cells far gone (won't respond to stim.)
Theocine best. but g.i. trouble

to its dilating the cerebral vessels. Kola preparations are often advised as general tonics in weakness and neurasthenia.

Caffeine has been used largely for its action on the heart and is often said to be a substitute for digitalis, though as a matter of fact, it cannot replace the latter, the action of the two on the heart being entirely dissimilar. In cases of heart weakness without marked dilatation and incompetency of the valves, it may be of service as it increases the activity of the ventricle, but its reputation in cases of cardiac disease is due mainly to the removal of dropsy through its diuretic action. The contraction of the arterioles following the use of caffeine may also be of service in feeble action of the heart.

In their action on the kidney the members of the caffeine series stand preëminent, no other drug producing such a copious flow of urine as either caffeine or theobromine. As has been explained already, the latter is to be preferred to caffeine as a diuretic, and may be used in all cases in which there is a pathological accumulation of fluid in the body, whether of cardiac, hepatic or renal origin. The results are most brilliant, however, in cases of cardiac dropsy, and here it may be prescribed along with one of the digitalis series. It must be emphasized, however, that in these cases it cannot supplant digitalis, but merely aids in the removal of the fluid which is obstructing the circulation by its pressure, while digitalis relieves the dilatation of the heart. In cases of hepatic dropsy, caffeine and theobromine have also proved of service, although here the treatment can only be considered palliative. In renal dropsy theobromine has been used with somewhat variable results; it does not seem to increase the albumin in the urine, but not infrequently little or no diuresis follows its administration. This is only to be expected where the renal cells are in such a condition as to be incapable of stimulation. Where the disease is less developed the members of this series produce the usual increase in the secretion.

Inflammatory effusions do not seem to be lessened to any marked extent by either caffeine or theobromine.

Theobromine in very large doses has been found to produce nausea and loss of appetite when taken for long, but in ordinary quantities it produces no symptoms save diuresis. Theocine has undoubtedly greater diuretic power than either caffeine or theobromine, and has been largely advertised for the treatment of dropsy. In a large proportion of cases it causes marked disturbance of the digestive organs, however, and in several instances epileptiform convulsions have followed its use.

Coffee and Tea.

Coffee is not used in medicine, but in view of its immense dietetic importance it may be mentioned here in what respects it differs from the pure caffeine. The coffee bean contains about two third per cent. caffeine, and the roasting does not seem to reduce the percentage at all, as was formerly supposed, and since almost all the caffeine is extracted by the ordinary culinary preparation, a cup of coffee con-

Cup coffee = 1½–3 gr + coffeon (like vol. oils)
Tea same + ta (esp. if prepared too long & green tea) may = chronic dyspepsia & const.
Wakefulness + relief from fatigue (central & on muscles).
Increases metabolism urea & CO2 exc. — no sparing of metabolism & no food value.

tains from 0.1–0.2 G. (1½–3 grs.) of caffeine. Along with the caffeine there are extracted a number of other substances, the most important of which are volatile substances, such as furfuralcohol, produced by the roasting; these have been called *Coffeon* and resemble in their action the volatile oils.

Tea contains a larger percentage of caffeine (about 1½–2 per cent.), but as less tea is used than coffee, each cup may be considered to contain 0.1–0.2 G. (1½–3 grs.). In green tea there is a considerable quantity of a volatile oil which also passes into the infusion, but this is not present in black tea, owing to the greater heat used in its manufacture. Both black and green tea contain about 7 per cent. of tannic acid, but this is only extracted slowly. The bitter taste in tea that has been prepared too long is due to the tannic acid passing into solution.

The wakefulness and the relief from fatigue which are produced by tea and coffee are undoubtedly due to the caffeine contained in them, and are to be ascribed to the central action chiefly, although its action on the muscles may also be of some value here. On the other hand, the feeling of well-being and comfort produced by coffee after a full meal is probably to be explained by the local action of the volatile oil in the stomach. The same result is produced by preparations of the other volatile oils, and, in fact, these are often added to coffee in the form of brandy and other liqueurs. Apart from this local action, the volatile parts of tea and coffee (theon, coffeon), seem to have no effect whatever on the economy. In experiments on the activity of the digestive ferments outside the body, it is found that caffeine increases slightly the rapidity of the process, but that coffee and tea retard it considerably. In experiments in which coffee and tea were introduced directly into the stomach of animals, the former was found to cause a transient rise in the secretory activity, while the latter arrested secretion at once; but it is possible that the psychical effect of the taste in man may alter this effect. Coffee is said to increase the peristaltic movements of the intestine, while caffeine has no effect on them. Tea that contains much tannic acid precipitates the peptones and albumins of the stomach, and may lead to chronic dyspepsia and constipation.

It was formerly stated that coffee lessened the tissue change and that it ought therefore to be included among foods, and one enthusiast even suggested that a diet of tea and coffee exclusively should be served out in the besieged fortresses of France in 1870. It has been shown conclusively, however, that far from lessening the metabolism of the body, coffee and tea increase it, the amount of urea and carbonic acid excreted being considerably augmented by their use. This is only to be expected from the increased activity of the nervous centres, which leads to increased movement and increased consumption.

Chocolate contains theobromine (0.5–1 per cent.), instead of caffeine, and besides this a large amount of fat (cacao-butter, 15–50 per cent.), starch and albumins. The theobromine does not possess the stimulant action of caffeine on the nervous system, and chocolate may

Chocolate = theobromine + food substances (starch, albumins + cocoa butter. If much oil = "heaviness" in stomach. Some detrimental effect on gastric mem – lessens appetite.

therefore be taken where coffee or tea produces wakefulness. The starch and fat are assimilated by the tissues so that chocolate is a true food. But Neumann finds that cocoa retards the absorption of the proteins and fats of the food, especially those forms of cocoa in which the fat has been partially removed. On the other hand, cocoa with a large percentage of oil delays the gastric secretion and may give rise to a feeling of heaviness and discomfort in the stomach. Its continued use may cause dyspepia, partly from this cause and partly from theobromine acting on the gastric mucous membrane. There is no question that the food value of cocoa and chocolate is often overestimated. It allays hunger, but this is only in part from its being a food, the local detrimental effect on the gastric mucous membrane tending to lessen appetite.

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X. CURARA.

Curara, woorara, urari or woorali, is an arrow poison used by the natives of South America, who prepare it by extracting various barks and plants. The plants used seem to vary somewhat in different localities, but those which produce the symptoms known as curara action are undoubtedly members of the genus Strychnos, such as S. toxifera.

Myoneural [illegible]

Curara paralyzes ~~motor~~ muscles terminations. No vol movements. Eventually resp ceases.
Heart fails from asphyxia. Frog may recover thru skin respiration.
Tie all leg but sciatic & curarize. Stim sciatic = response, no action [illegible] if stim muscle substance. Responds - so not muscle. Unligated leg in acid

response in ligated one - so not sensory. Must be in connection between motor ends & muscle [illegible]

Different preparations of curara were found by Boehm to contain different alkaloids. That formerly obtainable owed its activity to *Curarine,* but the curara now exported contains *Tubocurarine,* which resembles curarine in its action, and *Curine,* a weaker poison, which has an entirely different effect. Another preparation examined by him contained three alkaloids, *Protocurine, Protocuridine* and *Protocurarine,* the last of which is the most powerful of all the curara alkaloids. Most of the experiments on which the statements regarding curara action are based were performed with the crude drug, but the alkaloids seem to have a very similar effect, with the exception of curine.

Motor endings

Action.—The chief effect of curara is paralysis of the **Terminations of the Nerves Supplying Striated Muscle** or the **Myoneural Junction** and it therefore arrests all the voluntary movements. In the mammal the muscles give way one after the other until the animal lies helpless on the ground. It can still move its limbs, but cannot recover its ordinary position, and soon the limbs become totally paralyzed and the respiratory movements alone persist, although they too are slow, weak and jerky. Eventually the respiration ceases also and asphyxia follows, but is not betrayed by the usual convulsions, owing to the motor impulses being unable to reach the muscles. The blood, however, becomes venous, and the heart soon fails from the asphyxia and not through the direct action of the poison.

In the frog similar symptoms are seen, but here the arrest of the respiration is not necessarily fatal, as the skin carries on the exchange of gases, and recovery not infrequently occurs after two or even five days of complete paralysis. The cause of the curara paralysis was demonstrated by the classical researches of Claude Bernard and Kölliker. If the sciatic nerve of the frog be stimulated during the paralysis no movement follows, but if the artery of one leg be ligatured before the application of the poison this limb remains unparalyzed and reacts to reflex irritation, while the rest of the body is perfectly motionless. These facts can only be interpreted in one way; the paralysis is peripheral and not central, and may, therefore, be due to action either on the muscle, the nerve trunks, or the intermediate structures. That it is not due to the muscle is shown by the fact that direct stimulation causes the same movement as usual. On the other hand, in the experiment in which the artery is ligatured, stimulation of the nerves above the ligature, that is, where the poison has access to the nerve fibres, causes contraction, so that the nerve trunks do not seem affected. This may be shown in another way; if a nerve-muscle preparation be made and the nerve be laid in a solution of curara, contraction of the muscle still occurs on stimulation of the nerve, but if the muscle be laid in the curara solution stimulation of the nerve has no effect, while direct stimulation still causes contraction. Curara therefore acts on the connection between the nerve and muscle within the muscle itself and paralyzes it without previous stimulation.

Action on Nerve-ends.—Since the investigations of Bernard and Kölliker, the action of curara has been known to be peripheral, and it has been tacitly accepted that it could be localized in the anatomical structure known as the motor end-plates, and this belief has unques-

Poisons paralyze by making receptors incapable of function. Physiological fatigue the same, but here the receptor substance is used up. Heart unaffected. Resp. late ~~rhythm~~ periodic - time to recover.

tionably influenced the views as to the site of action of other alkaloids, such as atropine and adrenaline. Of late years facts have been accumulating which seemed difficult to reconcile with this view, and Langley has recently shaken its foundations by showing that curara continues to act after the muscle plate has lost its function. For the action of nicotine on the muscles is opposed by curara, not only in normal muscles, but also in those in which the nerves and nerve-endings have degenerated through section. The action of curara here must be exerted, not on the end-plate, but on some undegenerated substance, which has been termed receptive substance or receptor, and is believed by Langley to be in close connection with the actual contractile substance of the muscle fibre. The impulse from the nerve must be transmitted to the latter through this receptor, for otherwise the curara paralysis would be inexplicable, and the contractile substance must be capable of action after the receptor is paralyzed by curara. The new facts are unquestionable, and, although the old nomenclature of "nerve-ends" may be maintained until the position is further developed, this is only possible on the understanding that it does not indicate the actual anatomical nerve plate, but some body which does not degenerate with the nerve and is therefore peripheral to the true nerve plate and pertains to the muscle.

Here, perhaps, better than elsewhere it can be shown that the condition of "paralysis" produced by poisons is analogous to that termed by physiologists "fatigue." It is known that on stimulating a nerve rapidly by electric shocks, or otherwise, the muscle at first contracts with every stimulation, but eventually ceases to respond, owing to "fatigue" of the nerve ends, that is, to their inability to transmit impulses from the nerve to the muscle. If now the response to nerve stimulation of a muscle to which a minute quantity of curarine has been applied, be compared with that of a normal one, it is found that the poisoned one ceases to respond much sooner than the other—*i. e.*, its nerve ends become fatigued much sooner. The more curara is applied, the sooner does it fatigue, until at last no response at all can be elicited from it. The "paralysis" of the nerve terminations by curara then is of the same nature as physiological "fatigue," and other conditions of "paralysis" are also analogous to those produced by over-stimulation, though the exact condition of the paralyzed organ may not be the same as the fatigued one. Thus there is some reason to suppose that in the curarized terminations the substance which is normally consumed in transmission is present, but in a form which cannot be utilized, while in fatigue it has all been exhausted by the impulses which have already passed through.

Curara paralyzes very readily the terminations of nerves in all striped muscular tissue except the heart. The nerves first affected are those of the short muscles of the toes, ear and eye, later those supplying the limbs, head and neck, and, last of all, those supplying the muscles of respiration. At first slight movements can be performed, because single impulses can pass through the nerve ends, but sustained contractions such as are necessary to preserve the equilibrium, cannot be maintained, and the animal therefore falls. The intermittent impulses to the respiratory muscles still allow time in the interval for the recovery of the terminations, but as the intoxication lower and less marked action on unstriped muscle. Invertebrates immune. Fibres & muscle itself unaffected. Large dose paralyzes peripheral gang. hence they won't transmit impulses inaugurated centrally (or peripherally, sensory)

proceeds the number of impulses which can pass through becomes fewer and fewer, and the movement therefore assumes more and more the character of a jerk. Eventually total paralysis sets in and, unless artificial respiration is carried on, asphyxia follows. Small doses of curara do not affect the innervation of unstriped muscle, and the strict demarcation of its action is seen very distinctly in organs which consist partly of striated and partly of unstriated fibres. Thus in the œsophagus, the striated muscle fibres no longer contract on stimulation of the vagus after curara, while the unstriated continue to respond as usual. In the iris of the mammals, which consists of unstriated muscle, curara has no effect, while the striated muscle of the bird's iris ceases to respond to stimulation of the motor oculi, but contracts on direct stimulation. The terminations of the nerves in the heart are not affected, as the cardiac fibre is not of the same character as the ordinary striated one, but the nerves of the lymph hearts of the frog are paralyzed, these organs consisting of ordinary striated muscle. Curiously enough, it has been found that curara does not act on the terminations of the motor nerves supplying the electrical organ of the torpedo, although this organ is analogous to striated muscle in many respects. The nerve ends in striated muscle in invertebrates also appears to be immune to curara (Straub).

The nerve fibres seem unaffected by curara, for stimulation causes the usual electrical changes in them after it. The action of curara on the muscle fibres has been a good deal disputed, many authorities denying that any alteration whatsoever occurs, while others assert that slight modifications may be observed.

When larger quantities of curara or curarine are injected, several other organs are affected. Thus the **Peripheral Ganglia** cease to transmit impulses, and hence stimulation of the nerves central to them has little or no effect. In this way the stimulation of the vagus in the neck produces no slowing of the heart, because the impulses can no longer pass through the ganglionic structures on the course of the fibres, and stimulation of several secretory nerves, such as the chorda tympani, has no effect on the secretion. The sympathetic ganglia are also paralyzed by nicotine, which differs from curara in stimulating them previously, and also in attacking the ganglia before it affects the endings in muscle.

Large quantities of curara are often said to paralyze the nerve terminations in unstriated muscle, but this has never been satisfactorily proved, all the symptoms quoted to show this effect being explained by the paralysis of the sympathetic ganglia, which undoubtedly occurs.

Curara, then, first paralyzes the terminations of efferent or centrifugal nerves in voluntary muscle, and in larger quantities the ganglia (cf. Nicotine). The peripheral terminations of the afferent or sensory nerves seem unaffected, for if the artery of one leg be ligatured before the application of curara, reflex movements may be obtained in it from stimulation of any part of the body, while if the

CNS – & heart little affected. Large dose – heart up. Secretions increased
Rapidly eliminated from kidney as such. May be swallowed without harm (ext)
Action on muscle antagonized by physostigmine

sensory terminations were paralyzed reflexes could be elicited only by the irritation of parts to which the poison had not penetrated, *i. e.*, from the ligatured leg.

Very large quantities of curarine are said by Tillie to cause a stimulation of the **Central Nervous System** resembling that described under strychnine. In ordinary poisoning, however, no evidence of this stimulation is shown, as, although an increased number of impulses may be sent out, they cannot reach the peripheral organs, owing to the paralysis of the transmitting apparatus.

The **Heart** does not seem to be acted on directly by ordinary quantities of curarine, and the circulation is left intact long after the respiratory nerves have been paralyzed. Large quantities prevent the inhibitory action of the vagus, and the pulse is consequently quickened, but the blood-pressure often begins to fall at the same time, owing to the dilatation of the peripheral arteries through paralysis of the ganglia on the course of the constrictor nerves. After curara and curarine the movements of the **Intestines** are said to be increased. This was formerly supposed to be due to the asphyxia, but seems to be independent of it, for the increased peristalsis occurs even when artificial respiration is kept up, and, according to Nasse, the irritability of the bowel muscle is much increased by curara. A similar acceleration of the rhythmic movements of the spleen has been noted after curara by Shäfer and Moore.

The **Secretions** sometimes seem to be increased by curara, for tears, saliva and perspiration may be formed in considerable excess of the normal.

Metabolism.—The cessation of the ordinary movements after curara and under artificial respiration has generally been accompanied by a marked decrease in the oxygen absorption and the carbonic-acid excretion, but Frank and Gebhard state that this is not the case when the temperature is maintained by the application of heat. Sugar and lactic acid are often found in the urine after curara, but this is due to partial asphyxia and not to the direct action of the poison; the glycogen of the liver and muscles disappears from the same cause.

Curara is excreted by the kidneys apparently unchanged. It has long been known that this arrow poison may be swallowed with impunity, provided there is no wounded surface in the mouth or throat, and that it is therefore perfectly safe to suck the poison from a wound. This has been explained in various ways, some holding that the absorption from the stomach is so slow that the kidneys are able to excrete the poison as fast as it reaches the blood and that this prevents its accumulation in sufficient quantity to affect the tissues. Others suppose that the liver retains and destroys it and a third view is that it is rendered innocuous in passing through the stomach walls.

Rothberger has recently shown that curara and physostigmine are mutually antagonistic so far as the action on the nerve terminations in striated muscle is concerned, and a number of other alkaloids also appear to resemble physostigmine in this respect.

Dangers in therapeutics. Tetanus. hydrophobia strych convulsions

Curine, the second alkaloid found by Boehm in some specimens of curara, is a much less poisonous body than curarine. It possesses some action on the heart, the same appearances following its injection in the frog as after digitalin and veratrine, while in mammals the rhythm is slow even after paralysis of the inhibitory mechanism.

PREPARATIONS.

Curara, an extract of varying constitution and strength. The active constituents are freely soluble in acidulated water, and when used ought to be injected hypodermically. Before using curara in therapeutics it is always necessary to estimate the strength of the preparation by experiments on animals, and its application ought to be graduated, commencing with the smallest quantities and increasing them until the desired effect is attained. Neither curara nor its alkaloids are official.

Therapeutic Uses.—Curara has been used occasionally in various conditions of exaggerated movement, such as tetanus, strychnine poisoning and hydrophobia. The object is to lessen the movement by partial paralysis of the motor terminations. The respiratory nerves being the last to be affected by the poison, the convulsions may be controlled, or at any rate hindered from causing such marked irregularity of the respiration as they would otherwise do, and in the same way the overstrain of the heart caused by the convulsions may be prevented. The danger accompanying the use of curara is great, however, and the fact that in all these cases the cause of the movement is excessive activity of the central nervous system would seem to indicate one of the many depressants of that system, rather than a drug such as curara, whose action is on an entirely different part of the body. Some cases of tetanus and one of hydrophobia are alleged to have been successfully treated by it, but its use must still be regarded as purely experimental, and, in fact, as generally opposed to the teachings of rational therapeutics.

Paralysis of the terminations of the motor nerves in striated muscle—the so-called "**Curara-Action**"—is elicited by a large number of poisons, but in few of them is it the first effect of their application. Many drugs induce it only when injected in large quantities and at the end of a series of phenomena produced by their action on other parts of the body; it is observed much more frequently in frogs than in mammals, and is often of little importance compared to the other symptoms. Among the bodies which resemble curara more closely in their action, the peripheral paralysis playing the chief rôle in their effects, are the ammonium compounds formed from the natural alkaloids by the substitution of an alkyl, *e. g.*, methylstrychnine, amylquinine, etc.[1] Some of the ammonium salts and many of the alkyl ammonium combinations also cause it, and the corresponding compounds of phosphorus, arsenic and of several metals. Meyer ascribes this effect to the strong basicity of these substances. The simpler bodies, pyridine and quinoline which form the basis of most of the natural alkaloids, have little action save on the nerve ends.

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[1] Boehm has recently stated that tubocurarine, which is the active constituent of much of the modern curara, is really one of those methyl bases (methylcurine).

Nikolski u. Dogiel. Ibid., xlvii., p. 68.
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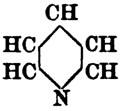
XI. CONIINE, GELSEMININE AND SPARTEINE.

Several alkaloids which show many points of resemblance to curara in their pharmacological effects, may be classed together, although their action may differ in details.

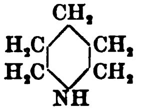
Coniine.

Coniine is one of the simpler derivatives of *Piperidine,* which is obtained from *Pyridine* by reduction. A series of alkaloids may be formed from piperidine by substituting methyl, ethyl, propyl or other alkyls for hydrogen, and one of these, α-propyl-piperidine, is the natural alkaloid coniine.

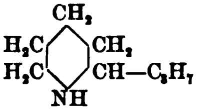
Pyridine.



Piperidine.



Coniine.



Coniine is found in Hemlock (Conium maculatum), along with two nearly allied alkaloids, *Methylconiine* and *Conhydrine.* The latter differs from coniine only in having a hydroxyl group in the side chain. Methylconiine is found in many specimens of coniine, and is probably formed in the plant, although this has not been definitely proved; in it the hydrogen attached to the nitrogen of coniine is replaced by methyl. Coniine is of some historical importance, as the first vegetable alkaloid which was successfully formed by synthesis in the laboratory. It is a volatile fluid, characterized by a strong mouse-like odor, but forms crystalline, non-volatile salts. The two other alkaloids of hemlock act in the same way as coniine, although much more weakly, so that the effects of the crude preparations of the plant are identical with those of coniine.

Piperidine and its compounds with methyl and ethyl act in the same way as coniine but more weakly. An ascending scale of toxicity may be formed, commencing with piperidine and passing upwards through methyl- and ethyl-piperidine to coniine. The other simple derivatives of piperidine seem to resemble coniine in their action as far as it has been investigated.

Symptoms.—The general symptoms induced in man by poisonous doses of coniine are weakness, languor and drowsiness which does not pass into actual sleep. The movements are weak and unsteady, the gait is staggering, and nausea and vomiting generally set in, along with profuse salivation. In most cases the intelligence remains clear to the end, as is related of the death of Socrates from hemlock poisoning, but in some instances imperfect vision and hearing have been noted. The pupils are somewhat dilated. Tremors and fibrillary contractions of the muscles are often seen in animals, and some observers state that actual convulsions occur. The breathing becomes weaker and slower and death occurs from its arrest.

Action.—Coniine is sometimes credited with possessing a narcotic depressant action on the **Central Nervous System,** but this is by no means a characteristic feature in poisoning, for in both man and animals consciousness is often retained until immediately before the cessation of the respiration. Other writers mention convulsions as a feature of coniine poisoning and weak convulsive movements are often seen before death, obviously from the failure of the respiration. Quite distinct from these are the twitching and tremors of the earlier stages of the intoxication, which are often accompanied by a certain stiffness and rigidity of some of the muscles of the limbs. Some of these movements may be due to the partial paralysis of the motor nerve terminations preventing the animal from contracting its muscles in a normal tetanus and permitting only of short, jerky movements, which may readily be mistaken for convulsions. Or they may indicate a preliminary stimulant action on the nerve ends or receptors in the muscles, similar to that observed in nicotine poisoning.

Coniine causes nausea and very often vomiting at an early stage of its action. This may be elicited by its hypodermic or intravenous injection, and is probably due to an alteration in the medullary centres rather than in the stomach. The nausea is accompanied by profuse salivation and sometimes by perspiration.

The chief effect of coniine in the frog is a paralysis of the **Termination of the Motor Nerves** similar to that induced by curara. This paralysis is elicited only with difficulty in the mammal, but unquestionably occurs to a more or less marked extent. According to some researches on the subject, all the symptoms in mammals are due to this action, but some writers regard both the convulsions and the final failure of the respiration as of central origin. It seems likely that while in the frog the symptoms all arise from the action on the nerve terminations, some of the phenomena observed in mammals are due to paralysis of the medullary centre of respiration. It is difficult to explain on any other theory how the symptoms of coniine poisoning are so different from those of curara.

Coniine acts on the **Peripheral Ganglia** in the same way as curara. According to some writers these are first stimulated and then paralyzed, and there seems to be no question as to the final paralysis, whether the preliminary stimulation is present or not. Coniine certainly does not act so strongly on the ganglia as nicotine, and the details of the action may, therefore, be left for discussion under that heading. (See page 272.) The inhibitory impulses no longer reach the heart after large doses of coniine, owing to paralysis of the ganglionic apparatus, and stimulation of the vagus nerve has no effect on the pulse rate. Some drugs which act on the extreme terminations of the inhibitory fibres still slow and weaken the heart, however. Similarly, stimulation of the cervical sympathetic no longer dilates the pupil, because the superior cervical ganglion is paralyzed. The partial dilatation of the pupil in cases of poisoning may, perhaps, indicate similar action on the ciliary ganglion.

Conine seems to have but little direct effect on the **Heart**, though large quantities slow the rhythm and somewhat prolong the systole in the frog (Moore and Row), and some slowing of the mammalian heart has been noted from the intravenous injection of large quantities. The inhibitory mechanism is often found to be stimulated and the pulse is accordingly somewhat slow and weak. The paralysis of the ganglia on the inhibitory nerve may lead to some acceleration in other cases, but the changes in the heart are not marked features in the intoxication.

Moore and Row have observed a very considerable though transient increase in the arterial tension after coniine, and regard it as of peripheral origin, for they found that the perfusion of coniine through the blood vessels of the frog tends to constrict them, while the direct application to the exposed blood vessels has no such effect, but rather widens their calibre. They are accordingly inclined to regard the rise of blood-pressure as due to a stimulation of the ganglionic apparatus lying on the course of the vaso-constrictor nerves.

The **Respiration** is generally accelerated and deepened in the earlier stages of the coniine intoxication, but later becomes slow and labored, then weak and irregular, and finally ceases while the heart is still strong and the consciousness has just disappeared. The cause of the asphyxia is still undecided, many investigators holding that the centre is paralyzed before the terminations of the nerves in the diaphragm, while the majority of recent investigators look upon the paralysis of those terminations as the cause of death.

A curious change has been observed by Gürber in the **Blood Cells** of frogs poisoned with coniine. Numerous small vacuoles appear in the red corpuscles, and persist long after the frog shows no further symptoms of poisoning. The nucleus is also somewhat altered, but not so characteristically.

Coniine is rapidly **excreted** in the urine, so that its action passes off very soon even when quite large doses are taken. The treatment of coniine poisoning therefore consists in evacuation of the stomach and artificial respiration.

Piperidine acts in the same way as coniine, but more weakly, while methyl- and ethyl-piperidine stand between them in toxicity. Many of the piperidine alkaloids cause the formation of vacuoles in the red blood cells of the frog, and the simpler members of the series act more strongly in this direction than the more complex ones, while they are much less active as general poisons.

Pyridine resembles piperidine in most features but does not paralyze the ganglia nor increase the blood-pressure. It seems more poisonous in frogs, and induces distinct depressions of the central nervous system, but like piperidine it is only feebly poisonous in mammals. Pyridine is excreted in the urine as methyl-pyridine, a combination between it and the alkyl occurring in the tissues. A similar synthesis occurs between methyl and telluric acid (see Tellurium).

Quinoline and isoquinoline cause in mammals a condition of collapse similar to that seen under the antipyretics and the benzol compounds.

PREPARATIONS.

Conium (U. S. P.), the dried, full-grown, unripe fruit of Conium maculatum, or hemlock.

Fluidextractum Conii (U. S. P.), 0.1–0.5 c.c. (2–8 mins.).

Therapeutic Uses.—Conium has passed into almost complete disuse. It has been prescribed in whooping-cough and chorea with doubtful results, and has been employed locally and given internally to relieve pain. Tetanus and strychnine poisoning have been treated with it without apparent results.

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Gelsemium.

Gelsemium sempervirens (Yellow Jasmine or Carolina Jasmine) contains two alkaloids, *Gelsemine* and *Gelseminine.*[1] Gelsemine forms crystalline salts, while gelseminine is entirely amorphous, and, as far as is known, does not form any crystalline combinations. Gelsemine is only slightly active, inducing the same symptoms in frogs as strychnine, but having no effects on mammals, even when injected into a vein in very large quantity. Gelseminine, on the other hand, is a powerful poison which resembles coniine in most of its effects. The action of the crude preparations of gelsemium is undoubtedly due to gelseminine and not to gelsemine, as far as mammals are concerned. Large quantities of the extract injected into frogs may, however, increase the reflex movements somewhat from the gelsemine they contain.

Action.—The symptoms of gelsemium poisoning resemble those of coniine so closely that the reader may be referred to the description given under the latter (see page 265). Gelseminine differs from coniine chiefly in possessing a more depressant action on the central nervous system. In the frog the spinal cord is distinctly less active than usual before the ends of the motor nerves are paralyzed, and, in fact, the depression of the central nervous system seems to be the cause of the general paralysis in these animals, rather than the peripheral action, although this is always present. In mammals the symptoms resemble those of coniine more closely than in the frog, and there may be some question as to whether the effects are mainly central or peripheral in origin. There is a general consensus of opinion, however, amongst those who have worked on the subject that gelseminine proves fatal by paralyzing the respiratory centre rather than the terminations of the nerves in the diaphragm and other muscles, while most writers now consider the asphyxia of coniine poisoning due to the peripheral action. The symptoms are practically identical, however, and it will probably be found that both act on the same points in the innervation of the respiration. In the meantime the question must remain undecided for both poisons.

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[1] Gelsemine is frequently known as gelseminine, a use of the term which leads to some confusion, and which is not based on the history of the drug.

The pupil is very widely dilated by gelseminine when a solution is applied locally to the eye, much less so in general poisoning, in which the respiration generally fails before the pupil is fully dilated. The power of accommodation is also entirely lost when gelseminine or gelsemium tincture is applied to the eye. This mydriatic effect has not been explained, but the most plausible suggestion would seem to be that gelseminine paralyzes the terminations of the oculomotor nerve in the eye in the same way as atropine. Gelseminine differs from atropine in its behavior to other nerves, however, for it paralyzes the inhibitory cardiac fibres and the chorda tympani through acting on the ganglionic structures on their course and not on the extreme terminations. Its action on the ganglia, as far as it is known, resembles that of coniine, but it does not cause any increase in the arterial tension, such as is observed under this poison.

PREPARATIONS.

Gelsemium (U. S. P.), **Gelsemii Radix** (B. P.), the dried rhizome and roots of Gelsemium sempervirens or nitidum.

Fluidextractum Gelsemii (U. S. P.), 0.05 c.c. (1 min.).

Tinctura Gelsemii (U. S. P., B. P.), 0.3–1 c.c. (5–15 mins.).

"Gelsemine" is an unofficial mixture of the alkaloids in very varying proportions. In some preparations no gelseminine whatever was found.

Therapeutic Uses.—The tincture of gelsemium has been employed as a mydriatic in ophthalmology, but it presents no advantages over the more generally used preparations of atropine, and sometimes causes some pain and redness, which has prevented its general adoption for this purpose. In certain forms of neuralgia, especially of the facial branches of the trigeminus, gelsemium has proved of some value, when administered internally as the tincture.

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Sparteine.

Another alkaloid which resembles coniine closely in its action is *Sparteine,* which is found in the common broom plant (Spartium or Cytisus scoparius), along with a neutral substance, *Scoparin.* Sparteine[1] is a pyridine derivative possessing the formula $C_{15}H_{26}N_2$, and is a fluid, but forms crystalline salts, which are often prescribed instead of the crude preparations.

Action.—The general effects of sparteine are almost identical with those of coniine, but it seems very probable that the central nervous system is little affected by it, the whole of the phenomena pointing to a paralysis of the motor nerve terminations and of the sympathetic ganglia. Sparteine has more effect than coniine on the heart, which it depresses, so that the rhythm is slow and the contractions weak. When injected into a vein, sparteine induces less increase in the arterial tension than coniine, probably because the contraction of the vessels is counterbalanced by the weakness of the heart. No increase in the arterial tension is observed from the administration of sparteine internally, and even the slight rise of pressure induced by intravenous injection is of only short duration.

The slow pulse and slight rise of pressure observed in experiments in animals when sparteine is injected intravenously have led some writers to ascribe to it an action similar to that of digitalis, and at one time sparteine was used to some extent as a substitute for the latter; both experimental and clinical observations, however, go to show that these claims are quite unfounded, and sparteine is comparatively little used at the present time, and possesses no properties which are likely to reinstate it in favor.

Sparteine is very much less poisonous than either coniine or gelseminine. It proves fatal to animals by paralyzing the terminations of the phrenic nerves in the diaphragm.

Broom tops have long enjoyed a certain reputation as a diuretic, and this perhaps strengthened the belief in the virtues of sparteine as a heart remedy. The diuresis is not due to the sparteine, however, but to the scoparin, which seems to act on the renal epithelium in the same way as uva-ursi and other remedies of that series. The broom tops are generally administered in the form of a decoction or infusion, and the large amount of water taken along with them may also tend to increase the urine and to strengthen the reputation of the remedy.

PREPARATIONS.

Scoparius (U. S. P.), **Scoparii Cacumina** (B. P.), the tops of Cytisus scoparius or broom.

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[1] Sparteine also occurs in the black and yellow lupines along with lupinine.

Volatile liquid alkaloid. In tobacco a vol. oil (usual action) which gives
odor, flavor & strength. Decomposed nicotine smells like tobacco. Lobeline resembles
nicotine

Infusum Scoparii (B. P.), 1–2 fl. oz.

Sparteinæ Sulphas (U. S. P.) ($C_{15}H_{26}N_2H_2SO_4 + 4H_2O$), colorless, white crystals with a saline bitter taste, very soluble in water and alcohol. The dose recommended by different clinicians as of benefit in heart disease varies from 0.004–0.8 G. ($\frac{1}{16}$–12 grs.) in the course of 24 hours. It may be given in doses of 0.1 G. (2 grs.) with perfect safety.

Uses.—Broom tops are used as a feeble diuretic, generally in the form of a decoction (16 G. in 250 c.c. of water, or ½ oz. in a half pint in divided doses in 24 hours), or infusion (B. P.). Sparteine has been advised in heart disease, but is of no value here. It has also been proposed to paralyze the terminations of the vagus with it before the administration of chloroform, the object being to avoid the reflex syncope, but a small dose of atropine would be preferable. It has also been suggested as a local anæsthetic in ophthalmology, but has only a feeble action.

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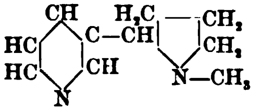
XII. NICOTINE AND LOBELINE.

Nicotine, the well-known alkaloid of tobacco (Nicotiana tabacum), is a volatile fluid, possessing a strong alkaline reaction, and forming salts with acids, most of which are amorphous. It is a combination of pyridine with a hydrated pyrrol ring as shown by the structural formula—



Nicotine is the only constituent of tobacco which possesses any toxicological interest, although several other alkaloids are present in comparatively small amounts. It is accompanied by a volatile oil in dried tobacco, but this is only developed during the processes of preparation and seems to have no action apart from that of the other volatile oils. The odor and flavor, and probably the "strength," of tobacco depends in part upon the quantity and quality of this oil, in part on some products of the decomposition of nicotine. Absolutely pure nicotine has comparatively little odor, but it decomposes when kept, becomes dark colored and acquires the characteristic odor of tobacco.

Another alkaloid which is practically identical with nicotine in its pharmacological action is *Piturine* ($C_{12}H_{16}N_2$), which is derived from the pituri plant (Duboisia Hopwoodii). The leaves of the pituri are said to be used by the Australian natives in the same way as tobacco by the civilized races.

Lobeline ($C_{18}H_{23}NO_2$), an alkaloid obtained from Lobelia inflata or Indian Tobacco, resembles nicotine very closely in its action, and may be discussed along with it.

Lobelia for asthma. No other uses. Act on C.N.S. of Sympt. gang. and myoneural junctions in voluntary muscle. Poisoning (acute): g.i. heart fast or slow, mental, clonic convulsions then tetanus. Or may be no convulsions but paralysis

Tobacco is not used in therapeutics, but is of great hygienic importance, and nicotine possesses considerable biological interest from the results obtained by Langley by its use in physiology in recent years. Lobelia has a somewhat restricted field of usefulness in therapeutics, in which it is prescribed in asthma. These alkaloids act chiefly on the central nervous system, the sympathetic ganglia, and the myoneural junctions in voluntary muscle.

FIG. 25.

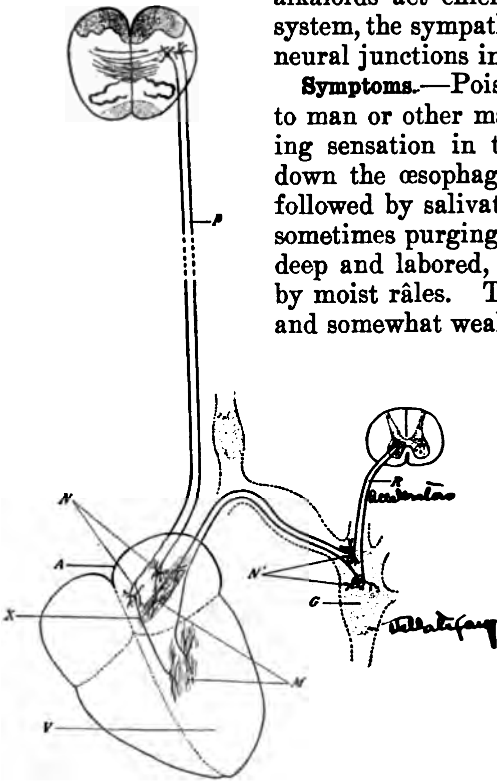


Diagram of the regulating nerves of the heart. *P*, inhibitory fibres arising in the vagus centre in the medulla oblongata and terminating around ganglion cells in the auricle (*A*). The axis cylinders issuing from these cells terminate on the muscular fibres of the auricle and ventricle (*V*). *R*, accelerator fibres issuing from the spinal cord and terminating around ganglion cells in the stellate ganglion *G*. The axis fibres of these ganglion cells run through the *Annulus Vieussenii* and terminate on the muscular fibres of the auricle and ventricle. *N*, *N'* points at which *nicotine, conine, curarine*, etc., ~~act—the ganglion cells surrounded by the terminations of the nerves. *M*, points at which *muscarine and atropine* act—the terminations of the fibres~~ which arise from the intra-cardiac ganglia.

Symptoms.—Poisonous doses administered to man or other mammals cause a hot, burning sensation in the mouth, which spreads down the œsophagus to the stomach, and is followed by salivation, nausea, vomiting and sometimes purging. The breathing is quick, deep and labored, and is often accompanied by moist râles. The pulse is generally slow and somewhat weak at first and then becomes very rapid, but after very large doses may be first accelerated and then slow and feeble. Some mental confusion, great muscular weakness, giddiness and restlessness are followed by loss of coördinating power and partial or complete unconsciousness. Clonic convulsions set in later, accompanied by fibrillary twitching of various muscles, and eventually a tetanic spasm closes the scene by arresting the respiration. In other instances the convulsions are followed by complete relaxation of all parts of the body, the reflexes disappear, the respiration becomes slow and weak and finally ceases, the heart continuing to beat for some time afterwards. Very large doses of nicotine may prove fatal within a few seconds; the symptoms are those of sudden paralysis of the central nervous system including the respiratory centre, and no convulsions are developed.

In the frog the same excitement and violent convulsions are seen as in mammals, but the respiration soon ceases, and there follows a "cataleptic" stage in which the animal assumes a characteristic atti-

Gang of X in heart stim at first (Curara & Coniine paralyze these gang. [illegible]
paralyze nerve terminations). Soon paralyzed then thus) X = acceleration as
accel. nerves have no gang. in heart.

tude. The fore legs are crossed in front of the sternum and are rigid, the thighs are at right angles to the axis of the body and the legs are flexed on them but are not rigid. When a leg is drawn down it at once returns to its original position, and the frog still attempts to escape when it is aroused. Fibrillary contractions are observed in many of the muscles. Somewhat later, the reflexes disappear, the muscles become flaccid, and eventually complete paralysis occurs from a peripheral, curara-like action.

Nicotine has but little toxic action on the lowest invertebrates, but as the nervous system begins to be differentiated it causes paralysis, and still higher in the scale the paralytic action is preceded by a stage of stimulation.

Circulation.—The action on the circulation is extremely complex, as a number of factors are involved. After moderate quantities the heart is slow and may stand still in diastole for a few seconds, but then recovers gradually and regains its former rhythm or becomes somewhat quicker. The slow pulse is due to stimulation of the ganglia on the vagus nerve (Fig. 25, *N*), exactly the same effects being produced as by stimulation of the vagus fibres in the neck. It is not affected by section of the cervical pneumogastric, as the path from the ganglia to the cardiac muscle fibres is still intact, but on the other hand, it is prevented by atropine, which acts on the extreme terminations of the inhibitory fibres, and therefore blocks the passages of impulses from the ganglia to the muscle. It is also prevented by a number of drugs, such as curara and coniine, which paralyze the ganglia.

This stimulation of the ganglia is of short duration, soon passing into paralysis, which obstructs the passage of the inhibitory impulses from above. On stimulating the vagus after nicotine there is consequently no slowing of the heart but often some acceleration, due to the fact that the accelerating fibres running along with the inhibitory in the vagus nerve have no ganglionic apparatus in the heart, and are therefore unaffected by nicotine. Although inhibitory impulses can no longer reach the heart from above, the intracardiac inhibitory neuron is still intact, and stimulation of the venous sinus in the frog still causes arrest of the heart exactly as in the normal animal. The stimulating current here reaches the inhibitory nerves beyond the paralyzed ganglia (Fig. 25, *X*), and these preserve their usual irritability. In the same way a number of poisons which act upon the extreme terminations of the inhibitory fibres in the heart muscle (Fig. 25, *M*) can slow the rhythm even after the ganglia have been paralyzed by nicotine (see the Pilocarpine and Muscarine group). The results of the stimulation and subsequent paralysis of the ganglionic structures on the inhibitory fibres by nicotine are the preliminary slowing and subsequent slight acceleration of the heart rhythm seen in both cold- and warm-blooded animals. In larger doses nicotine produces no slowing of the heart, owing to the ganglia being paralyzed immediately, without previous stimulation.

Inhib. center (stimulated as is, heart muscle, but later both paralyzed. Intravenous = rise in b.p. due to stim of [illegible] ganglia (then paralyzed) so high then low b.p. + (with plaques)

In addition to its action on the peripheral inhibitory ganglia, nicotine seems to stimulate the vagus centre in the medulla, as the slowing is greater when the vagi are intact than when they are divided. But apart from this action on the inhibitory apparatus, nicotine possesses some direct action on the heart muscle, which appears to be first stimulated and then depressed. Accordingly, when the inhibitory apparatus has been previously paralyzed, moderate quantities increase the rate of the heart beat considerably, while very large ones slow and weaken it. It has been supposed that this quickening is due to action on the accelerator centre, or on the ganglia on the course of the sympathetic accelerator fibres (*N'*, Fig. 25), but this seems not to be the only cause, for Wertheimer found the acceleration continue even after extirpation of these ganglia. The quickening must be attributed in part or wholly to action on the cardiac muscle, or on the terminations of the accelerator nerves in it. The subsequent slowing and weakness is undoubtedly due to a paralyzing action on the muscle itself.

On the injection of nicotine into a vein or subcutaneously, an immense augmentation of the arterial tension occurs; this may be due in part to stimulation of the vaso-constrictor centre in the medulla, but is to be ascribed chiefly to peripheral influences, for it has been observed after section and even after total removal of the spinal cord. The vaso-constrictor nerves pass through ganglia on their way to the vessels and the rise of the blood-pressure seems to be mainly caused by a stimulation of these ganglia.

The constriction of the vessels can be observed in many parts of the body —mesentery, foot, rabbit's ear, etc. In these parts the pallor produced by the narrowing of the vessels is followed by redness and congestion owing to the paralysis of the ganglia, and at the same time the pressure falls to a level somewhat below the normal. In some parts of the body no constriction of the vessels occurs; for example, the dog's lip and mouth are congested first and then become pale. This flushing seems partly due to the stimulation of the ganglionic apparatus on the vaso-dilator fibres for the lips and mouth, and partly to the constriction of the vessels in the splanchnic area diverting the blood current to these parts which are less abundantly supplied with constrictor fibres, for it occurs after removal of the superior cervical ganglion containing the vasodilator fibres.

After a few minutes the blood-pressure falls to the normal level or lower, but a second injection again produces a similar rise in the arterial tension, unless the first was large enough to paralyze the ganglia. Eventually nicotine lowers the blood-pressure, owing to the weakening action on the heart.

In the rabbit nicotine tends to induce lesions of the aorta with subsequent calcareous degeneration, which resembles the atheromatous patches seen in man. This is due to the very high blood-pressure, and similar effects are seen from adrenaline and from other measures which increase the blood-pressure, such as pressure on the abdominal aorta.

Respiration.—The respiration is at first rapid and shallow with some deficiency in the expiratory movements, but after a time, while maintaining the acceleration, it becomes deeper. It is liable to be inter-

Resp. faster then paralysis — death. Circ. continues, tho weak. Constriction then dil. of bronchi. If already constricted dil. at once. Stim. then paralysis of secretions — gang. — chorda tympani & sympathetic. Nerve distal from gang. may be cut off & action continue. Muscarine acts after nicotine paralysis, as stimulates nerve terminations beyond gang.

rupted at this stage by the convulsions, but if these do not prove fatal, it gradually becomes slower while remaining deep. Later, pauses in the position of expiration appear, and the movements become weaker until they disappear, the animal dying of asphyxia. The rapid, shallow movements in the beginning of the intoxication are absent in animals in which the pneumogastric nerves have been previously divided, so that this phenomenon has been ascribed to the alkaloid acting as an irritant to the pulmonary branches of the pneumogastric. The later features are caused by its acting on the respiratory centre directly, first stimulating and then paralyzing it. After large doses this direct action alone may be elicited. The paralysis of the respiration is the cause of death, the heart continuing to beat for some time afterwards although slowly and weakly.

The bronchial muscle relaxes after a transient constriction when nicotine or lobeline is ingested, these changes being brought about by stimulation and subsequent depression of the ganglia on the course of the innervating fibres. The dilatation of the bronchi is more marked when they have been previously in a state of constriction (Dixon and Brodie).

Most of the **Secretions** are increased temporarily by nicotine. The glands investigated have generally been the salivary, where it is found that the secretion is increased by the injection of small quantities, but is afterwards depressed, while large doses diminish it at once. The seat of action is again the ganglionic apparatus on the secretory nerves. If the chorda tympani be stimulated in the normal animal a large secretion of saliva at once follows, but if a sufficient quantity of nicotine be injected, no such effect follows its stimulation. If, however, the nerve fibres be stimulated between the ganglion cells and the gland (at X in Fig. 26), the secretion again follows as before. On the other hand, nicotine increases the secretion whether the chorda

FIG. 26.

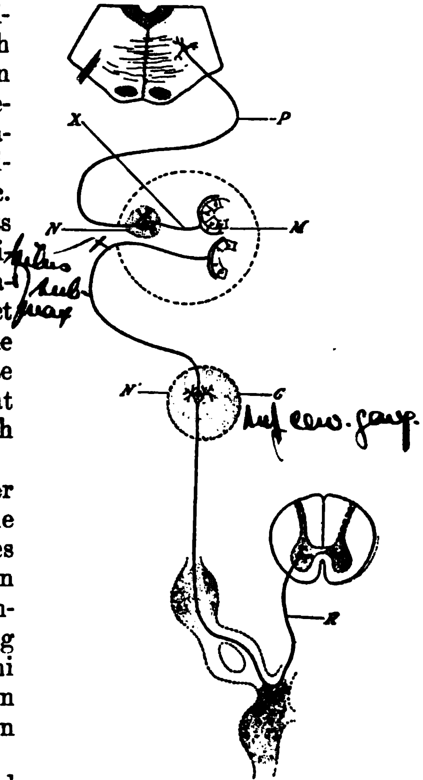


Diagram of the innervation of the submaxillary gland. *P*, a fibre of the chorda tympani issuing from the pons Varolii and after a devious course terminating around a ganglion cell in the hilus of the submaxillary gland. The axis from this ganglion cell runs to the secretory epithelium. *R*, a fibre issuing from the spinal cord and after running through the sympathetic chain in the neck, terminating around a ganglion cell in the superior cervical ganglion *G*. The axis from this cell runs to the secretory epithelium. In the diagram the nerves are represented as running to separate acini. *N*, *N'*, ganglion cells surrounded by the terminations of the nerves—the points at which *nicotine* acts. *M*, the terminations of the secretory fibres connected with the chorda tympani—the points at which *atropine*, *muscarine*, and *pilocarpine* act.

Ditto sweat bronchial etc. Urine — bile not under nervous control
small dose = emesis = purgation - due to G.I. movements — then tetany.
Ditto bladder & pregnant uterus

be intact or not, but ceases to act if the connection between the ganglion cells and the gland be interrupted. These results can only be interpreted by nicotine first stimulating and then paralyzing the ganglia on the course of the chorda tympani. In the same way it first stimulates and then paralyzes the ganglia which lie in the course of the sympathetic salivary fibres. Pilocarpine and muscarine cause profuse salivation after nicotine, because they stimulate the terminations of the nerves in the gland cells, and it is therefore immaterial whether the connection with the central nervous system be interrupted or not. On the other hand, the reflex secretion of saliva normally produced by irritation of the mouth or by chewing is prevented by nicotine. Atropine stops the secretion produced by nicotine by paralyzing the extreme terminations of the nerves.

The other secretory glands are affected in the same way by nicotine, and although the details have not been worked out so carefully as for the salivary glands, there is no question that their secretions are first increased by the stimulation of the ganglia on the course of their secretory nerves, and then lessened by their paralysis. Thus the sweat secretion is found to be markedly increased, as also the secretion of the bronchial mucous glands. The urine and bile have not been shown to be affected by nicotine, and as their secretion does not seem to be so dependent upon nervous influences, it is probable that it is but little changed in amount.

Nicotine produces extreme **Nausea** and **Vomiting** when taken even in comparatively small quantities, a fact which is generally recognized by tyros in smoking. This may be in part central in origin, but is mainly due to the powerful contractions of the stomach walls. This contraction extends throughout the intestinal tract, so that repeated **Evacuation of the Bowel** occurs. Somewhat larger quantities may lead to a tetanic contraction of the whole intestine with almost complete obliteration of the lumen. This exaggeration of the peristaltic contraction is probably due to stimulation of the motor nervous apparatus in the intestinal wall, and a subsequent paralysis of these structures leads to a failure of local stimuli to induce peristalsis. A further effect of nicotine in the bowel is due to its stimulating the ganglia on the fibres of the splanchnic which inhibit the rhythmical pendulum movements. These are arrested by the injection of nicotine, but return in exaggerated form as the ganglionic stimulation passes into paralysis. The mesenteric vessels are narrowed at first from stimulation of the ganglia on the course of the vaso-constrictor nerves, but congestion follows the depression of these ganglia and the consequent fall in blood-pressure.

Similar changes are produced by nicotine in the bladder which is thrown into tetanic contraction. The urine is therefore expelled very soon after the injection of nicotine and this probably gave rise to the erroneous view that the renal secretion was increased. The uterus is strongly contracted in pregnant animals, but is inhibited in the non-pregnant cat, in which the inhibitory nerves are more powerful than the contractor ones.

Eye – contr. then dil. n. v. acc as gangl ~~or~~ n symp stimulated. Muscle? then paralysis.
Nicotine causes stim then paralysis of ganglia (symp)

The action of nicotine on the **Pupil** varies in different animals, for while in the cat and dog its application either intravenously or locally produces marked but transitory dilation, in the rabbit partial constriction sets in immediately. In cases of acute poisoning in man contraction is generally seen at first and is followed by dilatation. In birds nicotine causes very marked contraction of the pupil, apparently owing to direct action on the muscle of the iris. The size of the pupil is regulated by two sets of nerves, the motor oculi and the sympathetic, and the ciliary fibres of both of these are interrupted by ganglia in their passage from the brain to the iris, those of the motor oculi by the ciliary ganglion, those of the sympathetic by the superior cervical ganglion (see Fig. 27, p. 288); the varying effects of nicotine may be due to its stimulating the one ganglion more strongly in one species of animals, the other in another. It is found, however, that atropine does not remove the effects of nicotine on the rabbit's eye, which would seem to indicate an action on the muscular fibres of the iris. Several other effects on the orbital muscles are seen; thus in cats and dogs the nictitating membrane is withdrawn, the eye opens and is directed forwards, while in the rabbit these symptoms are preceded by a stage in which the nictitating membrane is spread over the cornea and the eye is tightly closed. These are probably produced by action on the superior cervical ganglion.

Nicotine, then, first stimulates and later paralyzes all the **Sympathetic Ganglia**, whether applied locally to them or injected into the circulation. In these ganglia, the characteristic formation is the basket-like arrangement of the terminations of the entering nerve, which surround a large nerve cell from which an axis cylinder runs to the muscle or secretory cell. A nerve impulse from the central nervous system passes from the basket to the cell and thence to the periphery. Langley has recently shown that small quantities of nicotine stimulate the cell of the peripheral neuron, for the same effect is obtained from the application of the poison to the ganglion whether the basket-like terminations round the cell are normal or have degenerated. This renders it probable that the paralysis of the ganglia observed from larger quantities of nicotine is also due to action on the cell and not on the terminations.

In the frog nicotine produces fibrillary twitching and slow, prolonged contraction of the muscles, which are not prevented by previous division of the nerves leading to them, but disappear on the injection of curara; on the other hand, the paralysis induced by curara may be partially removed by small quantities of nicotine. This indicates that the fibrillary contractions arise neither from action on the central nervous system nor on the contractile substance of the muscle itself. And Langley has recently shown that the fibrillary twitching and slower contractions occur in muscles in which the nerve ends have degenerated from division of the nerves, so that nicotine acts on some receptive substance peripheral to the anatomical nerve ends. This is paralyzed by larger amounts of nicotine in the normal animal and the

Convulsions due to increased excitability of cns - of medulla. Sym. paralysis - resp. & v.m. reflexes. Excreted by urine. Detoxified by liver? Tolerance. Cross tolerance with Lobeline

muscle no longer contracts on stimulation of the nerve. Nicotine, therefore, acts on some receptor lying in the path of the nerve impulses from the nerve ends to the contractile substance of muscle and first stimulates it to activity and later paralyzes it. A similar effect is seen in reptiles and birds; in mammals the twitching of the muscles is prevented by section of the nerves, and is, therefore, due to central action, but large quantities of nicotine cause paralysis exactly like curara. The nerves of the orbital muscles are found to be paralyzed sooner than those of the rest of the body.

Nicotine does not seem to act on **Muscular Tissue** in general, although some obscure symptoms have been ascribed to changes in the cardiac and iris muscle.

The convulsions seen in both cold- and warm-blooded animals evidence the influence of nicotine on the **Central Nervous System.** The spinal cord is thrown into a condition of exaggerated irritability, and the reflexes are correspondingly increased, but the convulsions do not seem to be due so much to the spinal cord as to the medulla oblongata and hind brain, for they are not tonic but clonic in character, and are much weaker after division of the cord immediately below the medulla than in the intact animal. The medullary stimulation also betrays itself in the rapid and deep respiration, and is perhaps in part responsible for the inhibitory slowing of the heart and the rise in the blood-pressure. The higher centres in the brain seem to participate but little in the stimulant action of nicotine, which is short-lived, and soon gives way to marked depression of the whole central nervous system, manifested in the slow respiration, the low blood-pressure, the disappearance of the reflex movements and the final unconsciousness.

The **Excretion** of nicotine is probably carried on mainly by the kidneys, for it is found in the urine very soon after it enters the blood. It has also been detected in the saliva and perspiration. It has been shown repeatedly that nicotine and some other alkaloids are weakened in toxic effect or rendered entirely inactive by being mixed with an extract of the liver or of the suprarenal capsules; but no satisfactory explanation is forthcoming, though there is every reason to suppose that much of the nicotine absorbed from the stomach and intestine is thus modified in its passage through the liver.

When small quantities of nicotine are ingested repeatedly, the body soon gains a certain **Tolerance,** and no symptoms whatever are produced by doses which would in ordinary cases produce grave poisoning. A familiar example of this tolerance is seen in the practice of smoking. The first use of tobacco is in the great majority of individuals followed by vomiting and depression which may even amount to collapse, but after a few experiences no symptoms follow smoking, owing to the cells of the body becoming tolerant of the poison. In some individuals no such tolerance is developed, and in every case the tolerance is much more limited and more difficult to acquire than that for morphine. In animal experiments it is often found that while one application of nicotine produces considerable ganglionic stimula-

Tinct Lobelia – 1-4 cc. Preparations vary. Nausea with ~~[illegible]~~ bronchial secretion & relaxation of bronchial muscle for asthma.

tion, the second has much less effect. This is probably due, not to the establishment of tolerance, but to the first dose having produced primary stimulation and then depression of the ganglia, this depression, while not amounting to complete paralysis, being sufficient to counteract to some extent the stimulant action of the second injection. True tolerance is attained very imperfectly by animals from the use of repeated small doses, but when larger amounts are used some tolerance is soon acquired (Edmunds).

Nicotine and Piturine are not used in therapeutics. Tobacco was formerly employed in the reduction of intestinal hernia, and for this purpose was injected into the rectum in the form of an infusion. Several cases of poisoning and the introduction of general anæsthesia led to its disuse.

Lobeline ($C_{18}H_{23}NO_2$), the alkaloid of Lobelia inflata or Indian Tobacco, possesses almost exactly the same action as nicotine, and animals which have acquired tolerance for nicotine also resist the action of lobeline (Edmunds).

Preparations.

Lobelia (U. S. P., B. P.), the leaves and tops of Lobelia inflata, U. S. P., the dried herb, B. P.

Fluidextractum Lobeliæ (U. S. P.), 0.5 c.c. (8 mins.).
Tinctura Lobeliæ (U. S. P.), ~~1–4 c.c. (15~~–60 mins.). 1–4 cc.
Tinctura Lobeliæ Ætherea (B. P.), 5–15 mins.

Therapeutic Uses.—Lobelia was formerly used as an emetic, but is exceedingly depressant and unreliable, and if vomiting does not occur, is liable to give rise to the most alarming symptoms of poisoning. The only condition in which it is now used at all is spasmodic asthma, which appears to arise from paroxysmal contraction of the bronchial muscles. Its action certainly supports this use of the plant, but perhaps it aids in these conditions as much by the increased secretion of the mucous membranes owing to the nausea as through its action on the motor nerves of the bronchial muscles. Its effects must be carefully watched, as the preparations seem to vary in strength, and alarming symptoms and even fatal results have sometimes followed its use.

Tobacco.

Tobacco had been in use among the aboriginal tribes of America before they became known to civilization. It was introduced into Europe soon after the discovery of America, and its use as an article of luxury, beginning in England, soon spread to the continent, and in spite of papal bulls and numerous efforts on the part of the secular authorities, has continued to enthral a considerable portion of the human race. The most widespread use of tobacco—smoking—is also the most ancient one, having been that of the aboriginal Indians. Snuff-taking, introduced by Francis II. of France, remained fashionable for a long time, but is now almost obsolete. Tobacco-chewing is a more modern development, but shows no signs of abatement. Curiously enough, the leaves of the pituri plant, which, as has been mentioned, contain an alkaloid nearly allied to nicotine, are formed

In smoking nicotine absorbed, but probably has no action.
Pleasure ~~due~~ to nicotine or not? Chronic troubles – nose & throat
excessive secretions – alkaline vapor & heat. Nicotine swallowed in
saliva =

and loss of
appetite & emaciation. [illegible] mechanism affected – irregularity of pulse & palpitation.

into a mass and chewed by the natives of Australia. In smoking, snuffing or chewing, nicotine is absorbed. It has been stated and the statement has received an undeservedly wide circulation, that tobacco smoke contains no nicotine but merely the products of its decomposition; but as a matter of fact, tobacco smoke, whether from cigars or pipes, contains a certain amount of the alkaloid itself, along with pyridine and many of its compounds. The amount of nicotine in tobacco smoke cannot be definitely stated, as it depends on the kind of tobacco, as well as on the way in which it is inhaled; but a large proportion of that contained in tobacco passes over in the smoke. In snuff the nicotine is generally small in amount, while in chewing tobacco there is generally a varying amount of foreign matter, such as molasses. The enjoyment derived from the use of tobacco has never been explained, and it is not even proved that nicotine is essential to the pleasurable results; consideration of the pharmacological effects of nicotine gives no clue, for these are of the opposite nature. It has been suggested that smoking gives repose and thereby improves intellectual work, but this is denied by many habitual smokers. It has also been stated and denied that the mental energy is reduced by the use of tobacco, and an attempt has been made to demonstrate this by measuring the amount of work done with and without tobacco; but investigators are not agreed on the results, which probably depend largely upon the individual. One fact is certain, that the tobacco habit cannot be compared with the use of such drugs as morphine, cocaine, or alcohol, for it is not taken with the purpose of producing stimulation or depression of the central nervous system, and it seems doubtful whether the nicotine ordinarily absorbed really has any action whatsoever.. Perhaps the local effects on the mouth, nose and throat play a larger part in the effects of tobacco than is generally recognized. A certain amount of rhythmic movement demanding no exertion seems in itself to have a soothing, pleasure-giving effect, for it is otherwise impossible to explain the satisfaction enjoyed by many in chewing tasteless objects, such as gum or straws. A curious fact which tends to show that tobacco smoking is not carried on for the sake of the nicotine absorbed is that the pleasure derived from a pipe or cigar is abolished for many persons if the smoke is not seen, as when it is smoked in the dark.

Most people may indulge in the moderate use of tobacco for many years with perfect impunity, but its excessive use is followed in many individuals by a number of symptoms, some of them trivial, others indicating grave changes in important organs.

One of the commonest effects of overindulgence in tobacco is a chronic inflammation of the throat and upper parts of the respiratory passages, leading to hoarseness and excessive secretion of the mucous glands. This is explained by the constant application to the throat of an irritant, alkaline vapor, and is probably not due to the specific action of nicotine. A similar irritated condition of the tongue is frequently met with, more especially when the hot vapor is constantly

Retinal changes. Tremor, muscular weakness Dyspnoea
Even nervous degenerations. Symptoms disappear on withdrawal
Rarely "abstinence symptoms".

directed on one part, as in pipe smoking, and it is sometimes stated that the constant irritation thus produced renders the tongue and lip more liable to cancerous disease. Dyspepsia, want of appetite, and consequent loss of flesh may also be explained by the local irritation produced by the nicotine swallowed in the saliva. A common result of the abuse of tobacco is palpitation and irregularity of the heart, which has been attributed to changes in the inhibitory mechanism. Another important symptom is dimness of vision, especially for colors, and imperfect accommodation, which may go on to complete blindness in one or both eyes. In early cases the retina often appears pale, and if the condition persists, atrophy of the optic nerve may result, probably following on degenerative changes in the ganglion cells of the macular region of the retina. The hearing is said to be affected by excessive smoking, but the symptoms are indistinct and variable. Smoking causes a slight rise of blood-pressure in some individuals, and this has aroused apprehensions that it may tend to favor arteriosclerosis, but the change is so slight that these fears are quite groundless. Nervous symptoms, such as tremor, exaggeration of the reflexes, headache and giddiness, are sometimes developed in workmen in tobacco factories, but they do not seem to be induced by smoking or chewing tobacco, though depression, muscular weakness and giddiness are sometimes complained of. In the great majority of cases of chronic tobacco poisoning, the symptoms disappear on abandoning the habit, or even on restricting the daily consumption. A series of subjective and even objective symptoms are said to be induced in neurotic subjects by the sudden withdrawal of tobacco.

Esser has recently stated that chronic nicotine poisoning in animals induces marked disturbance of the heart, and that degeneration of the vagus fibres are recognizable histologically; changes have also been found in the nerve cells of the spinal cord and sympathetic ganglia similar to those described under chronic alcoholic poisoning.

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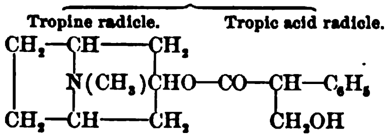
Atropine close related to cocaine. Hyoscyamine isomer of atropine
" " " hyoscine or scopolamine
" atropine. Homatropine an artificial tropine

XIII. THE ATROPINE SERIES.

The atropine series contains a number of very closely allied alkaloids, of which the chief are *Atropine, Hyoscyamine* and *Hyoscine* or *Scopolamine.* They are found in several plants of the Solanaceæ order, and in most cases several of them occur together.

Atropine may be broken up by the action of alkalies into an alkaloid, *Tropine,* and *Tropic Acid.* The former is a pyridine compound very closely allied to *Ecgonine* (see cocaine) as may be seen by its structural formula, while the latter is an aromatic acid.

Atropine.



Atropine and hyoscyamine are isomers, and in fact atropine has recently been shown to be a mixture of equal parts of hyoscyamine and dextro-hyoscyamine, which differs from the ordinary or lævo-hyoscyamine in the direction in which it rotates a ray of polarized light. The action of atropine is thus compounded of the action of these two bodies, which differ very greatly in their pharmacological effects, although they are almost identical in their reactions to chemical reagents. Hyoscyamine is very readily changed to atropine, and this generally occurs to a large extent in the process of extraction from the plants.

Hyoscine or *Scopolamine* was formerly supposed to be another isomer of atropine, but has lately been shown to differ slightly in its formula, which is $C_{17}H_{21}NO_4$. It is very closely allied to atropine, and is decomposed into tropic acid and *Scopoline* (*Oscine*), which is nearly related to tropine, but differs from it in the number of hydrogen and oxygen atoms.

A number of other alkaloids have been described in different plants, generally associated with one or more of those already mentioned. But on examination these have generally proved to be mixtures of atropine, hyoscyamine and hyoscine. Thus the *Duboisine* of Duboisia myoporoides, the *Mandragorine* of Mandragora (Mandrake) and the *Daturine* of Datura stramonium have all failed to maintain their position as new bases and have proved to be mixtures of the established alkaloids in varying proportions. *Atropamine,* a new alkaloid found by Hesse in some species of Belladonna, differs slightly in formula from atropine, from which it may be formed by the application of heat; it is decomposed into a substance which is isomeric with tropine, but which differs from it in some respects and which has been called *β-tropine.* Atropamine is isomeric but not identical with *Belladonnine,* which is a compound of yet another isomer of tropine, *bellatropine.* *Pseudo-hyoscyamine* is said to differ from atropine and hyoscyamine in some of its chemical relations, but has not been the subject of much work as yet. *Atroscine* is isomeric with scopolamine, and the same relation appears to exist between them as between atropine and hyoscyamine.

After atropine had been found to be a compound of tropine and tropic acid, a number of other acids were attached to tropine in the same way as tropic acid. These artificial alkaloids are known as *Tropeines,* and in action resemble atropine in some points while differing from it in others. Further study of the action of these tropeines is exceedingly desirable, and promises to be of considerable value in practical therapeutics. The only artificial tropeine which has as yet been used in medicine is the compound of tropeine and oxytoluic acid known as *Homatropine.* *Scopoleines* have been formed by substituting other acids for the tropic acid of scopolamine, but none of them have proved of value in therapeutics as yet.

It must be understood that the combination of tropine and its allies with tropic acid does not partake in any way of the nature of the combination of an ordinary alkaloid, such as morphine, with an acid. The bond is the much closer one seen in the compound ethers, and the resulting substance is alkaline and combines with acids to form salts exactly as other alkaloids do.

The chief plants containing these alkaloids are the following: Atropa Belladonna (Deadly nightshade), containing varying quantities of hyoscyamine and atropine,[1] hyoscine, and sometimes atropamine and belladonnine.

Hyoscyamus niger (Henbane), containing hyoscyamine and hyoscine, with smaller quantities of atropine.

Datura Stramonium (Thornapple), containing atropine, hyoscyamine, and some hyoscine.

Of less importance are:

Duboisia myoporoides, containing hyoscine and hyoscyamine, together with pseudo-hyoscyamine and other alkaloids. Another species of Duboisia contains piturine, an alkaloid nearly allied to nicotine.

Scopola atropoides, containing hyoscyamine and hyoscine, and perhaps small quantities of atropine.

Mandragora autumnalis, or Atropa mandragora (Mandrake), containing hyoscyamine with traces of other alkaloids.

A number of other Solanaceæ—*e. g.*, tobacco and potato leaves, are said to contain small quantities of one or other of these alkaloids but the quantity present here is too small to be of any importance. A ptomaine formed by the decomposition of fish and meat and known as ptomatropine also produces symptoms closely resembling those of atropine poisoning, but has not been isolated as yet.

These alkaloids all resemble each other closely in the effects produced by them in animals. Some differences in the symptoms exist, however, and the action of atropine alone will first be described and later the points in which that of hyoscyamine and of hyoscine differ from it.

Atropine acts as a stimulant to the central nervous system and also affects a number of peripheral organs; in some of these the changes

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[1] The relative proportion of atropine and hyoscyamine in all these plants is not known, as hyoscyamine is very often changed to atropine in the process of extraction.

Stim. to C.N.S. + peripheral action. Dry skin & throat, thirst, hard to swallow & talk
vomiting, light headache, pupils dil., resp. & pulse up. Skin hot. Restlessness, delirium
mania, convulsions. Usually coma & asphyxia (centers depressed)
early action - increased reflex irritability & medulla. A true stim. of higher brain.
Talking & delirium ~~[illegible]~~ than [illegible] [illegible] = end.

are due to the interruption of nerve paths, while in others these remain intact under atropine.

Symptoms.—In man and the higher animals small toxic doses cause dryness of the skin and throat, thirst, difficulty in swallowing and hoarseness in speaking. There is often nausea and in some cases vomiting, headache and giddiness; the pupils are wider than normal and the sight may be indistinct, especially for near objects. The respiration and pulse are quickened, or the latter may at first be somewhat slowed. A symptom that is often present, though by no means invariably so, is redness of the skin, more especially of the head and neck; the conjunctiva may also be congested. After larger doses the same symptoms are observed, but are soon followed by others of graver import. The patient can no longer swallow, although suffering from intense thirst, the heart is generally extremely rapid, speech is difficult and hoarse, and the pupils are dilated until the iris almost disappears. Restlessness and garrulity point to an increase in the irritability of the brain; the patient at first talks in a perfectly normal way but soon becomes confused, begins a sentence and does not finish it, often bursts into laughter or tears, and in short becomes delirious and eventually maniacal. Often marked tremor of different muscles may be observed, and eventually convulsions set in and may be the cause of death through the failure of the respiration. As a general rule, however, the stage of excitement passes into one of depression, the patient sinks into a sleep, which deepens into stupor and coma, the respiration and heart become slow, weak and irregular, and death eventually occurs from asphyxia.

In the frog the injection of small quantities of atropine is followed by a stage of increased reflex excitability, exactly resembling that seen under strychnine. It is generally of short duration, however, and is followed by a stage in which the frog lies motionless and does not react to stimulation in any way. After a variable time, sometimes a few hours, oftener several days, a return of the first symptom occurs, the reflex being much exaggerated and the tonic convulsions described under strychnine being generally developed. This stage slowly passes off and the animal again becomes normal.

Action.—These symptoms, both in mammals and amphibians, indicate stimulation of the **Central Nervous System** followed by depression. Those observed in man sometimes resemble those seen in the excitement stage of alcohol poisoning, and it has been suggested that in both the cause is rather a lessening of the control normally exercised by the higher powers over the lower motor areas than a true stimulation of the latter. But this is shown to be incorrect by the fact that in atropine poisoning the motor area is more easily stimulated by the electric current than normally. The stimulant action of atropine is also seen in the increased reflex response to irritation of the skin, as well as in the augmented activity of the centres in the medulla. The nervous symptoms under atropine, therefore, arise from true stimulation of the central nervous system, but they are wholly different

Cells on motor part of brain — controlling centres not active enough. Of lower
cord affected. Stimulated, then paralysis. Caffeine, highest psychic brain. Strychnine
cord. Salivary sweat, gastric, mucous, pancreatic & milk secretions lessened due to
nerve depression (peripherally). Paralyzes secretory terminations of chorda tympani.
[illegible] fibres still react to stim. And sympathetic fibres still active.
This paralysis of secretory terminations the mechanism of atropine gland action.

from those produced by strychnine, because the latter acts more especially on the lower parts of the nervous axis, while atropine acts more strongly on the higher divisions. The most marked symptoms of strychnine poisoning arise from the spinal cord and medulla oblongata, and consist in increased reflex movements and convulsions, while those caused by atropine are rather to be referred to the brain, and consist in increased coördinated movements, such as talking and delirium, the exaggerated reflex being of minor importance. In the frog the same effects are produced by each, because, the higher parts of the central nervous system being less developed than in the mammals, the first symptoms produced are those arising from the cord.

Atropine differs from caffeine, on the other hand, in its effect on the brain, for under the latter the psychical functions are those affected first of all. It would seem probable, then, that each of these three stimulates the whole of the central nervous system more or less, but that while strychnine acts more strongly on the lower divisions, the spinal cord and medulla, and caffeine on the highest functions, the psychical, atropine occupies a midway position, and exercises its chief action on the motor divisions of the brain. These are rendered so excitable that the controlling areas can no longer keep them in check, and an increase in movement occurs somewhat resembling that seen when the controlling areas are paralyzed by alcohol. The stimulant action spreads downwards when large quantities have been absorbed, and involves the medulla oblongata and spinal cord, so that symptoms resembling those seen in strychnine poisoning may make their appearance. After the stimulation has lasted some time, depression sets in and may go on to complete paralysis of the central nervous system. This is fatal to mammals through cessation of the respiration, but in the amphibia the paralysis may pass off after some time as the poison is excreted, and the stage of stimulation is renewed. Even during the stimulation stage some symptoms of depression are to be made out, exactly as has been described under strychnine.

The peripheral action of atropine involves a number of secretory glands, organs containing unstriped muscular tissue, and the heart.

Most of the **Secretions** are decreased by the application of atropine —salivary, gastric, pancreatic, mucus, milk and sweat. This is due, not to any action upon the secretory cells, but to the failure of nervous impulses. It has been investigated most carefully in the salivary glands, but enough work has been done on the others to show that the process is the same in all. The *secretion of saliva* in the normal animal seems to occur only when impulses reach the gland cells by one of two paths—through the chorda tympani, or through the cervical sympathetic fibres. If the chorda tympani be divided and put on electrodes and a canula be passed into Wharton's duct, a rapid flow occurs through it on stimulation of the nerve, which ceases or is very much diminished on stopping the stimulation. If now atropine be injected, stimulation causes no increase in the secretion and atropine, therefore, seems to paralyze some part of the peripheral secretory apparatus. The chorda tympani passes through ganglion cells on its way to the gland cells, and the impulses might be hindered in their passage through these, as actually occurs under the action of some drugs. (See Nicotine.) But this is not the explanation of the inefficiency of chorda stimulation, as is shown by the fact that if the electrodes be pushed into the hilus of the gland so as to stimulate the nerve fibres beyond the ganglia no secretion follows. Another explanation would be that the gland cells themselves are paralyzed by atropine, but this is shown not to be the case, for on stimulating the sympathetic, which supplies the same cells as the chorda tympani, the usual secretion follows. The site of action of atropine, therefore, seems to lie between the ganglion cells on the course of the chorda tympani and the secretory cells, that is, the point of attack is the terminations of the nerve fibres in the gland cells. The action is limited to certain definite terminations, for it has been noted already that the sympathetic secretory fibres are not paralyzed, and it was discovered by Heidenhain that not all the fibres of the chorda tympani are acted on by atropine. On stimulation of this nerve in the unpoisoned animal, besides the increased secretion, a redness and swelling of the gland is noticed, its temperature rises, and the blood escapes from the veins in much larger quantity than usual and in spurts as if from an artery. This is due to the dilatation of the arterioles of the gland from the stimulation of vaso-dilator fibres which run along with the secretory fibres in the chorda tympani. These fibres are not paralyzed by an injection of atropine, for on stimulation of the chorda afterwards the same symptoms are produced as before, save that no secretion occurs. Atropine then seems to select the terminations of the secretory ~~fibres of the chorda tympani for paralysis and to leave~~ all others unaffected. The secretion of saliva seems to occur generally ~~only on the arrival~~ of impulses by way of the chorda tympani, so that on the paralysis of its terminations the secretion ceases entirely.

In the same way the other *glands of the mouth, throat, nose and respiratory passages* cease secreting after atropine, and the effect is the characteristic dryness of the mouth, the hoarseness of the voice, and the thirst and difficulty in swallowing complained of after its administration.

The secretion of the *gastric juice* has recently been shown to be diminished or entirely arrested by atropine, which paralyzes the terminations of the secretory fibres of the pneumogastric nerve in the stomach. The hydrochloric acid of the secretion is more reduced than either the pepsin or the fluid as a whole. The secretion of *pancreatic juice* is reduced after atropine and stimulation of the pneumogastric has no effect on it, while in the normal animal it accelerates the flow. This has been attributed to the paralysis by atropine of secretory terminations in the pancreas, but it has been suggested that it may be an indirect result of the action of atropine on the gastric glands; these, as is well known, secrete when the vagus is stimulated, and their acid secretion passing into the duodenum, gives rise to the

No control of glycogen (governed by coeliac plexus). Milk chiefly dependant on chemic. Kid. & lymph not under much nervous control. All unstriped muscle (but vessels') movements lessened by atropine. III paralyzed – so no tone & = dil. local action & constitutional.

formation of secretin which in turn arouses the pancreas to activity; when the secretory fibres in the stomach are paralyzed by atropine, this chain is interrupted. It is possible that the pancreatic secretion is reduced by atropine in both of these ways. It is not entirely arrested because the secretin already formed continues to be absorbed and to act on the cells. The *bile* is also said to be somewhat lessened by atropine. The production of *sugar* from the glycogen of the liver has been recently shown to be controlled by branches of the cœliac plexus, but these have no effect after atropine, so that the terminations of the nerves in the liver cells seem to be paralyzed also.

The same paralysis is produced in the terminations of the nerves in the *sweat glands.* Stimulation of the sciatic nerve as a general rule produces perspiration in the foot of the cat and dog, but after atropine this effect is absent, because the impulses cannot reach the cells through the paralyzed terminations, and the skin therefore becomes dry and hot. The secretion of *milk* bears the same relation to that of perspiration as that of the pancreatic juice does to the saliva; it is increased by stimuli from the central nervous system, but at the same time the mammary gland continues to secrete after all its nerves have been divided. Atropine therefore lessens the secretion by paralyzing its nerves, but does not stop it altogether. The solids of the milk seem rather increased than diminished by the drug.

The *kidney* is not controlled so directly by nervous influences as the glands hitherto discussed, and atropine causes little or no change in the amount of urine except what is probably the indirect result of the arrest of the other secretions. The *secretion of lymph* is not altered by atropine, so that it is probably not controlled by nerves in the same way as the true secretions.

All **Organs Containing Unstriped Muscle** (apart from the arterial wall) seem to be altered by atropine. Thus the movements of the pupil and œsophagus (except in animals, in which these consist of striped muscle), stomach, intestine, bladder, uterus, spleen and thoracic duct are lessened by atropine.

The dilatation of the *pupil* by atropine has been the subject of a very large number of researches both by physiologists and by practical ophthalmologists. It occurs on internal administration as well as on the application of minute quantities locally, and is due to paralysis of the myoneural junctions in the circular muscle of the iris. This is shown by the fact that stimulation of the motor oculi nerve or of the postganglionic fibres from the ciliary ganglion is without effect. This limits the paralysis to the periphery, and that the muscle is not acted on is shown by its reacting to electrical stimulation. The local nature of the action may be further shown by carefully applying a minute quantity of the drug to one side of the cornea, when dilatation of one half or less of the pupil occurs, the rest remaining contracted. The motor oculi (Fig. 27) constantly transmits impulses through the ciliary nerves to the sphincter muscle of the iris and keeps the pupil moderately contracted, and when these impulses can no longer reach

Cocaine [illegible] sympathetics

the iris owing to the interruption of the path, the sphincter relaxes and the pupil dilates. The contractile substance does not seem to be affected by the ordinary application of atropine, but if strong solutions be continuously applied, it may be paralyzed by it as by many other drugs. Atropine antagonizes the action of pilocarpine in the pupil after degeneration of the motor oculi, and the receptor for these alkaloids therefore does not undergo degeneration and cannot be situated in the nerve ends but rather in the muscle between the nerve ends and the contractile substance.

Fig. 27.

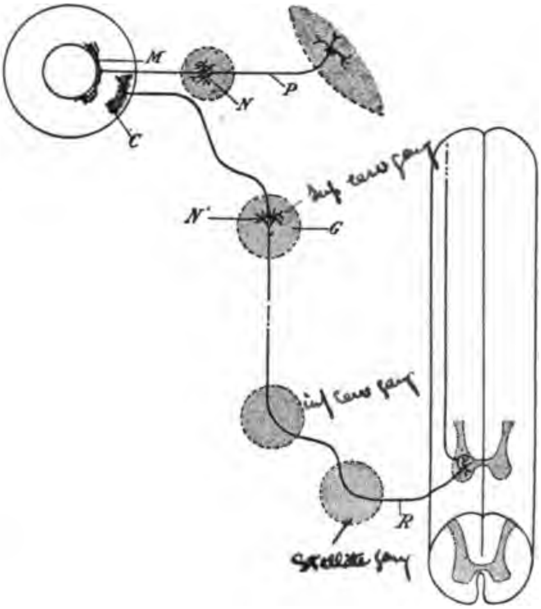


Diagram of the innervation of the iris. *P*, a fibre of the motor oculi passing from the brain to the ciliary ganglion (*N*) in which it terminates around a nerve cell, which sends an axis cylinder to terminate, *M*, in the circular fibres of the iris. *R*, a spinal nerve fibre issuing from the lower cervical cord, running through the stellate and inferior cervical ganglia and terminating around a ganglion cell in the superior cervical ganglion, *G*. The axis cylinder from this nerve cell runs to the iris (passing the ciliary ganglion) and terminates, *O*, on the radiating fibres. *M* indicates the terminations of the nerve fibre in the circular fibres, and is the point acted on by atropine and muscarine. *NN'*, the ganglion cells, is the seat of action of nicotine. *O*, the terminations in the dilator fibres, that of cocaine.

The constrictor muscle is constantly opposed by dilator fibres, and when the former is thrown out of activity by the paralysis of the terminations of the motor oculi, the radiating fibres cause an active dilatation. If, however, the radiating muscular fibres be separated from their innervating centre by section of the cervical sympathetic nerve in the neck, they also cease to contract and there is no active dilatation, so that atropine causes less widening of the pupil than it would if impulses continued to reach the radiating muscle. After the application of atropine to the eye, the iris often relaxes with sufficient force to tear weak adhesions to the lens, and if the iris be attached at two points to the lens, atropine causes a bow-shaped dilatation between them,

No light reflex · impulse can't reach muscle. [illegible] of [illegible] : further dil
Action on myo-neural junction of ciliary muscle paralyzes accommodation (larger dose
dil = increased intraocular tension.

the concavity being directed inward. The dilatation is therefore an active movement, accomplished by the contraction of the radiating muscular fibres, but these are not put in motion by the action of atropine on the radiating muscles of the iris, or their nerves, but by the normal impulses descending from the central nervous system, which after atropine are not counterbalanced by impulses reaching the circular fibres.

In short, the evidence goes to prove that atropine dilates the pupil by paralyzing the myoneural junctions in the circular muscle. This leaves the radiating fibres unopposed, and they therefore draw back the edge of the iris. The terminations of the nerves in the radiating muscle fibres do not seem to be affected by atropine.

The dilatation of the pupil effected by atropine is not quite maximal, for stimulation of the cervical sympathetic trunk generally increases it, though but slightly. It differs considerably in different animals, being more complete in man, the dog and the cat than in the rabbit, entirely absent in birds and reptiles and elicited with difficulty in the frog. In birds and reptiles the iris consists of striped muscle fibres, and accordingly atropine has no action on the nerve terminations.

In the rabbit and in man the dilatation is sometimes preceded by a slight contraction due, it is believed, to an irritant preparation setting up a reflex from the conjunctival sensory nerves. When complete dilatation is attained, the pupil ceases to contract in bright light, as the impulses descending from the central nervous system are prevented from reaching the muscle, although the rest of the reflex arc is intact.

Besides the dilatation of the pupil, a further result of the application of atropine to the eye is the paralysis of the *accommodation.* Near objects are no longer seen clearly, while distant ones are as distinct as formerly or may be even more distinct in some eyes. The action is here again on the myoneural junction, in this case in the ciliary muscle. On local application the relaxation of the lens occurs later, and disappears earlier than the dilatation of the pupil, and larger quantities are required to produce it.

The *intraocular pressure* undergoes a considerable augmentation after the local application of atropine as well as when it is applied through the general circulation. This is due to the dilatation of the pupil, and is a well-known result of the application of atropine in ophthalmology. It may, perhaps, explain the pain and aching in the eye and the headache complained of in some cases of poisoning, while in others these may be due to bright light falling on the retina, which is unprotected by the iris.

The terminations of the nerves in the unstriped muscle of the *œsophagus* seem to be affected in the same way as in that of the iris. A curious contrast has been noted by Luchsinger in the behavior of the œsophagus in rabbits and cats, in the former of which the muscle is striated, while in the latter the upper part is striated, the lower is unstriated. Atropine, he found, paralyzes the vagus in those parts

esophagus' unstriped muscle paralyzed - difficulty in swallowing (?)
bronchial muscles relaxed. Sedative to G.I. Prevents griping & puntive
of pilocarpine & muscarine. Gastric constipation. Action here not on N.
But Auerbach's plexus 2 increased regular peristalsis. Bladder, uterus & spleen muscles
relaxed. Rhythmic contractions of ureters.

which are unstriped, while leaving unaffected those in which the fibres are striped. Exactly the opposite occurs after curara, which paralyzes the nerve supply of the striped muscle, while leaving the unstriped active.

It is possible that the difficulty in swallowing, which is so well marked in cases of poisoning by atropine, may be due in part to the paralysis of the motor nerve, but it is generally attributed to the absence of the mucous secretion and consequent dryness of the passages.

Dreser has shown that the stimulation of the pneumogastric does not cause contraction of the *bronchial muscle* after atropine, while in the unpoisoned animal it has this effect.

Atropine has generally a sedative effect on the movements of the *stomach* and *intestine*, though vomiting is not infrequently observed in cases of poisoning, and less often free evacuation of the contents of the bowel. After very small quantities the normal peristalsis is not affected, and the movement induced by ordinary doses of the purgatives is not arrested, but the griping pains resulting from large doses or from the more violent purgatives are absent or less marked if atropine is given along with them. Similarly, the violent peristaltic and tetanic contractions seen after such poisons as pilocarpine and muscarine are prevented by the preliminary injection of atropine. These results suggested that atropine paralyzed the terminations of some of the extrinsic nerves of the stomach and bowel in the same way as it paralyzes the oculomotor terminations in the iris. But this proves to be incorrect, for the vagus and splanchnic nerves continue to exert their ordinary influence after atropine. In fact, these small doses of atropine appear to arrest only certain abnormal violent forms of contraction, and as it does this without interfering with the normal peristalsis and without interrupting the path of nervous impulses from the spinal cord to the bowel, it must be accepted that these abnormal forms arise from some mechanism which is distinct from that presiding over the ordinary peristalsis, and which does not lie on the path of the nerve impulses.

Somewhat larger quantities of atropine tend to increase peristalsis and this probably accounts for the vomiting and purgation that are occasionally seen in cases of poisoning. Magnus considers that the alkaloid causes this increased activity through its action on Auerbach's plexus, as this effect disappears when the muscle is dissected free from the nerve plexus. Finally, very large quantities paralyze the muscle fibres, but this probably does not occur in the intact animal.

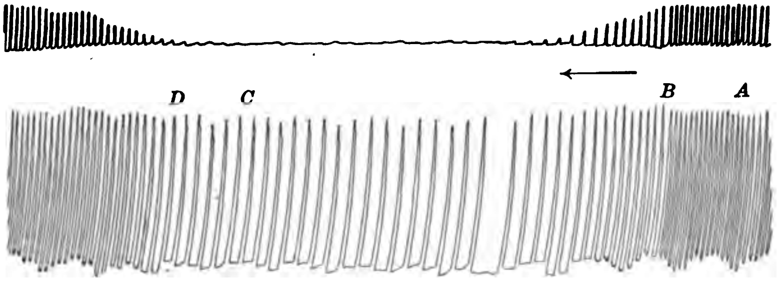
Atropine exercises the same sedative effect on the movements of other organs as on those of the bowel. Thus, the *spleen, uterus* and *bladder* react like the stomach and bowel, several poisons failing to induce contractions, while stimulation of the nerves continues to be effective. It has been observed frequently in cases of poisoning that the urine is ejected soon after the ingestion of the poison, and subsequently there is a desire to micturate without the ability to do so. The preliminary contraction of the bladder would seem analogous to

X terminations in heart paralyzed so X tonus lost & rate way up except in young children & aged. Stim. of X now means stim. of accelerators so rate still greater. In large dose, heart directly depressed.

that of the intestine, and the subsequent inability to empty it to the diminution of the peristalsis. The rhythmical contractions of the *ureters* are said to be accelerated by small doses, but to be slowed and arrested by larger amounts.

Atropine paralyzes the **Inhibitory Terminations of the Vagus in the Heart,** and stimulation of this nerve therefore causes no changes in the pulse after its administration. A number of other drugs also remove the inhibitory power of the vagus, but act on a different part of the nerve, namely, on the ganglia. That atropine does not act here but on the terminations has been shown by a number of observations.

FIG. 28.



Tracings of the ventricle (lower) and auricle (upper) of the dog's heart. During systole the levers moved upwards; during diastole, downwards. At *A*, the heart was normal; at *B*, the inhibitory fibres were stimulated electrically, and this was continued throughout the tracing. The ventricular rhythm became slow and irregular, while the auricle stood still in diastole. At *C*, atropine sulphate was injected into a vein, and at *D* the effects of the inhibition began to pass off, although the stimulation was continued.

Thus, in the normal frog's heart, and even after paralysis of the ganglia on the course of the vagus, electrical stimulation of the venous sinus causes slowing and standstill of the heart, because the stimulus reaches the vagus beyond the paralyzed ganglia (Fig. 25, p. 272); but after atropine, no slowing follows stimulation of the sinus. Again, several drugs stimulate the ends of the vagus in the heart and act on parts in which no ganglia exist, but these drugs have no effect whatever after atropine. Small quantities of atropine have no further action on the heart than the paralysis of the inhibitory nerve ends. The terminations of the accelerator nerve are unaffected, exactly as the terminations of the sympathetic in the salivary glands, and the heart muscle is neither stimulated nor depressed. The heart is therefore placed in the same position as if the vagus were divided in the neck, and, accordingly, is accelerated in some animals, while in others the rhythm is unchanged. In the dog there is a marked quickening of the heart after atropine, because normally impulses are constantly transmitted from the inhibitory centre in the medulla, and these prevent the heart from beating as rapidly as it would if freed from the nervous control. In the cat the tone of the vagus is less, and the changes produced by atropine are correspondingly smaller, while in the rabbit and frog there is generally no inhibitory retardation of the heart, and atropine therefore produces little change. In man the effects vary considerably with the age of the patient. The inhibitory fibres seem almost inactive at birth, but their tone increases with age up to 25–35 years, and from this time lessens again and is very slight in old age. Atropine does not quicken the heart in the newborn child, but up to about 30 the acceleration increases with the age, and from this point onwards it lessens again until the heart is accelerated by only 4–5 beats per minute in patients between 80–90 years. Along with the acceleration of the pulse the other effects of vagus section are also produced—increase in the extent of systole, decrease in the diastole and augmentation of the output of the heart per minute.

Stimulation of the vagus causes no retardation of the pulse after atropine, but on the contrary, is not infrequently followed by acceleration from the presence of accelerator fibres which are not affected by atropine.

Large quantities of atropine, besides paralyzing the vagus, weaken and depress the heart muscle, and the contractions consequently become slower and weaker and the output of the heart is less than normal.

The peripheral action of atropine hitherto discussed is due to its paralyzing receptors in a number of organs. Some of these are normally put in action by nerve impulses, which they transmit to the contractor or secretory cells, and their paralysis by atropine leads to the failure of part of the nervous control of the organ (many glands, pupil, bronchial muscle, œsophagus and heart). In other organs the receptors do not lie in the path of nerve impulses and their paralysis by atropine therefore does not affect the nervous control of these organs (muscle of stomach, intestine, spleen, uterus and bladder). The effects of atropine on these organs is in fact only detected by the cessation of movement due to certain poisons which cause contractions, presumably from stimulating the same receptors as atropine paralyzes.

A further question is whether the receptors are paralyzed at once or whether they undergo a short stimulation first. In favor of the latter theory several facts may be mentioned, as that the heart in mammals is often first slowed and then quickened by atropine; this may however be due to the inhibitory centre in the medulla being stimulated before the terminations are paralyzed. The increase in the intestinal movements, which occurs immediately after the injection of atropine, might also be cited as proof of the preliminary stimulation of the receptors. In the eye a short stage of contraction of the pupil not infrequently precedes the dilatation, but it is generally believed to be due to a reflex from the application of an irritant solution to the conjunctiva.

Several alkaloids stimulate the same peripheral receptors which atropine paralyzes, and the interaction of the two groups is of considerable importance. It is more profitably discussed after the general action of these poisons has been learned, and will be taken up at that point (see muscarine, pilocarpine and physostigmine; compare also nicotine and the curara and coniine series).

The voluntary **Muscles** are not directly affected by atropine. The terminations of the motor **Nerves** are depressed in the frog by large doses, but this has not been elicited in mammals by ordinary methods

Vol muscle unaffected. Locally sensory nerves depressed. Ointment or plaster not internally. High rate + v cons = high bp. (counteracted to some extent by v. dil of skin + depressed heart in large doses. Resp stops before heart stim of cns. = better + deeper resp. Depression finally.

of experimental investigation.[1] The terminations of the sensory nerves are depressed by its local application. Thus, when a liniment or ointment containing atropine is applied to an irritated surface, numbness is produced and the sensation of pain is lessened. This local anæsthetic effect is not elicited by its internal administration.

Circulation.—The effect of atropine on the circulation is somewhat complex, as, besides the action on the heart, that on the central nervous system must be considered. The heart is sometimes slowed and weakened at first, but is generally quickened from paralysis of the inhibitory fibres in the heart, and after very large doses is weakened by the direct action on the muscle fibre. The blood-pressure is often increased by the augmented output of the accelerated heart, and also owing to stimulation of the vaso-constrictor centre in the medulla, which contracts the arterioles in the abdomen. The constriction of these vessels is accompanied by a dilatation of the arterioles of the skin, from excitation of the vaso-dilator centre, so that the blood tends to flow from the abdominal cavity to the more superficial parts. The dilatation of the skin vessels is, however, insufficient to counteract altogether the contraction of those of the abdomen, so that some increase in the arterial tension often follows the ingestion of atropine. Larger doses of atropine lower the pressure immediately from action on the heart, and even small doses may have this effect. The dilatation of the skin vessels is more especially seen in the head and neck, and here produces marked flushing and a rash somewhat resembling that of scarlet fever. That it is due to central action is shown by the fact that it is prevented by division of the sympathetic trunk in the neck. The rash usually disappears after a few hours, but is sometimes followed in a day or two by desquamation. The circulation always persists after the respiration has ceased, and its failure is not the cause of death therefore.

The action of atropine on the **Respiration** has been the subject of much discussion in recent years. It is sometimes slower at first through some unexplained central action, but then becomes quicker, and according to most observers also deeper, and the amount of air inspired per minute is considerably increased. This is due to stimulation of the respiratory centre, which undergoes the same changes as the rest of the central nervous system. After large doses this quickened breathing is frequently interrupted by convulsive movements, and such an interruption often proves to be final. If it returns, the movements become shallower and slower in the stage of depression of the nervous centres, and the failure of the respiration is the cause of death in fatal cases of poisoning.

Atropine often induces a marked rise in **Temperature**, the cause of which cannot be said to be definitely known. According to Ott the dissipation of heat is increased, but the heat formation undergoes a

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[1] Some action on the myoneural receptors in voluntary muscle is shown to be exerted by atropine, for the twitching induced by physostigmine may be arrested by small quantities.

eat center excited + no sweat.
hyoscyamine (never pure (+ atropine) changes to atropine. Central action same
peripheral 2x strong.

still greater augmentation. This seems to be independent of the circulatory changes and also of the convulsions, and is attributed by him to direct action on the heat centres of the brain.

Atropine is **Excreted** in the urine in small quantities when injected into the dog, but most of it undergoes complete oxidation in the tissues; in the rabbit this seems to be the fate of the whole of the drug, for none is found in the excretions.[1] Young animals withstand much larger quantities than adults, according to v. Anrep, because the brain is less highly developed and the cerebral symptoms are therefore produced less easily. Rabbits may be fed for weeks on belladonna leaves exclusively without showing any symptoms of poisoning, while carnivorous animals and man are very much more sensitive to its action. A curious case of poisoning is related in which the defence was made that the alkaloid was taken accidentally through partaking of roast rabbit, the animal's flesh having been saturated with atropine through feeding on belladonna leaves. It was found that rabbits thus fed might, in fact, contain large quantities of atropine and yet show no signs of poisoning. Von Anrep succeeded in developing a certain degree of **Tolerance** in dogs through repeated administration of atropine, but it was very incomplete. The symptoms arising from the central nervous system were much less evident after a few doses, while those from the heart, pupil and secretory glands persisted after the treatment had been continued for some time.

Hyoscyamine is rarely obtainable in pure form, as it is almost always mixed with atropine, into which it changes when kept in solution and perhaps even when dry. It paralyzes the same peripheral mechanisms as atropine, but acts almost exactly twice as strongly on them. Its action on the central nervous system in mammals resembles that of atropine and the fatal dose is the same, but in the frog it has less tendency to cause convulsions. No narcotic influence is exercised on either frogs or mammals; the belief that it induces sleep is founded on observations in which hyoscine was mixed with the hyoscyamine employed.

The action of atropine, as has been stated, is compounded of that of natural or lævorotary hyoscyamine with that of its dextrorotary isomer. The latter does not exist free in nature and possesses only a feeble action on the nerve terminations, while it stimulates the spinal cord of the frog more than either atropine or hyoscyamine. The peripheral action of atropine is thus due to its containing hyoscyamine, and as a grain of atropine contains only half a grain of hyoscyamine the former naturally exercises only half the effect of a grain of hyoscyamine. On the other hand, the half grain of dextrorotary hyoscyamine in a grain of atropine is almost inert on the nerve terminations, but exercises the same effect on the central nervous system as its lævorotary complement. Atropine thus acts on the central nervous system in mammals in the same strength as hyoscyamine, but only half as strongly in the periphery.

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[1] Traces have been found in the milk of some animals and also in the fœtal blood.

Scopolamine same as hyoscine. Peripheral action same as atropine. Not enough given to act on heart. Mydriasis & loss of accommodation quickly + returns quickly. CNS = fatigue, drowsiness, normal sleep 5-8 hrs. drowsy 3 more hrs. Larger doses = ~~excitement~~, delirium etc. [illegible] 1/100 gr. Tolerance. Stronger peripheral action than atropine

Scopolamine, or **Hyoscine**, resembles atropine closely in its peripheral action. The inhibitory terminations in the heart are paralyzed, although the therapeutic dose in man is too small to elicit this effect and the pulse is therefore unaltered in rate or may be slower, owing to the hypnotic action. It produces mydriasis and loss of accommodation more quickly than atropine, but for a much shorter time; pure hyoscine acts about twice as strongly on the nerve terminations as atropine, or about equally strongly with hyoscyamine. The effects on the central nervous system present the greatest divergences from those described under atropine, for the characteristic stimulation is absent in the great majority of cases. As a general rule, scopolamine produces a marked sensation of fatigue and drowsiness, and the patient moves about less and speaks less. Soon an overpowering desire to sleep is felt, and a condition in no way dissimilar to the natural sleep follows. In many cases, however, a short stage of excitement with giddiness, uncertain movements and difficult and indistinct speech precedes sleep, and occasionally symptoms exactly resembling those produced by atropine follow the administration of hyoscine, especially if large doses are employed. Sleep generally lasts from 5–8 hours, and the patient may then remain in a somnolent condition for several hours longer. As a general rule, after small doses no confusion is complained of on awakening, but dryness of the throat and thirst are often present. Larger doses do not cause deeper sleep but give rise to delirium and excitement resembling those following atropine.

In one or two cases collapse has been observed after scopolamine. The vasomotor and respiratory centres do not seem to be stimulated as by atropine, the blood-pressure falling and the respiration generally becoming slower from the beginning.

In the lower mammals scopolamine reduces the excitability of the motor areas as tested by electric shocks, while the reflex excitability in the frog is not increased as by atropine. Hyoscine appears to be excreted or destroyed in the tissues much more rapidly than atropine, for its effects last a shorter time.

The action of hyoscine, then, seems to correspond with that of atropine, save that the central nervous system is here depressed, while the action on the peripheral nerve ends is stronger. It depresses the brain in very small quantities, ½ mg. (1/120 gr.) being generally sufficient to cause sleep. It does not seem to be so dangerous as the others of the series, for a dose of 5 mgs. (1/12 gr.) has been recovered from in man, and over half a gramme (7½ grs.) administered to a small cat did not kill the animal. A certain degree of tolerance is produced after repeated use, so that the dose has to be increased after a week or two.

It must be remarked that the action of hyoscine as a hypnotic differs considerably from that of opium and of the members of the methane series; it is very much less reliable and the sleep produced resembles much more nearly natural sleep. This difference has not been explained, but it seems probable that the seat of action differs in all three.

omatropine - quicker mydriasis & off sooner. less complete. less increase in intraocular tension.

Hyoscine is lævorotary to polarized light; the racemic form, which is often present in commercial hyoscine, acts only one half as strongly on the peripheral organs, because in it the lævorotary alkaloid is mixed with the dextrorotary isomer, which is almost inactive. The cerebral action is equal however in the two forms.

The **Other Natural Alkaloids** have been less carefully examined than the three foregoing; such mixtures as duboisine of course combine the effects of their constituents. The pseudo-hyoscyamine of Merck seems to be very feebly active, causing dilatation of the pupil on local application, but having little or no effect when given internally.

Among the **Artificial Tropeines** only one has received much attention at the hands of either experimental or practical therapeutists. This **Homatropine**, a compound of tropine and mandelic acid, which is found to be less poisonous than atropine but to resemble it in the symptoms produced by an overdose. The mydriatic effects pass off much sooner than those produced by the usual solutions of atropine, and are said to appear more rapidly and to be less complete. Homatropine causes less increase in the intraocular tension than atropine.

Several other tropeines have been examined by Falck and Gottlieb, who found that they varied a great deal in their action on the lower animals. Many of them produce no paralysis of the oculomotor or the vagus terminations, while others act here in the same way as atropine, but differ from it in power. It may be stated that in general the compounds of tropine with the acids of the methane series possess much less of the peripheral atropine action than the others. It was formerly believed that even the compounds with the aromatic acids were devoid of this action unless the acid possessed a hydroxyl group, but this general statement has been shown to be erroneous by Gottlieb's work. A considerable variation also exists in the effects of the tropeines on the central nervous system, some causing excitement like atropine, while others act as depressants and therefore resemble hyoscine.

As has been mentioned, many of the tropeines cause no paralysis of the vagus inhibitory terminations but they often act as stimulants to the frog's heart. Tropine itself is a weakly toxic, basic substance, which in large quantities possesses this cardiac action, but does not paralyze the vagus nor the oculomotor terminations on local application. After the injection of large quantities, dilatation of the pupil has been observed, it is true, but this does not seem to be of the same origin as that produced by atropine.

Some artificial scopoleines have been examined recently by Schiller, who found that they differed from scopolamine in being devoid of action on the nerve ends in the pupil and heart and on the salivary secretion. They possess a certain stimulant effect on the heart muscle like some of the artificial tropeines, and all produce more or less depression of the central nervous system and narcosis.

Methylatropine (Eumydrin) is said to possess the peripheral action of atropine but to paralyze the central nervous system. Its effects on the pupil in 5 per cent. solution are similar to those of atropine in 1 per cent. solution.

The action of the **Crude Drugs** is very similar to that of the active principles already discussed. The peripheral action of all of them is therefore almost identical in kind, though varying in degree. In considering their effects on the central nervous system it must be remembered that those containing much atropine are more stimulant, those with hyoscine more sedative. In belladonna preparations the quantity

Crude drugs vary as proportion of atropine & hyoscyamine (cns. stim) or hyoscine (cns. depression)

of hyoscyamine varies a good deal, and it is said that no atropine is present in the fresh plant, but that during the various processes of extraction some or all of the original hyoscyamine becomes changed to atropine; the relative proportion of these two poisons probably varies in different preparations, therefore. In hyoscyamus and scopola the presence of scopolamine produces a much more narcotic effect than is obtained from belladonna, while datura is generally said to be less sedative than the former, but less stimulant than the latter. Duboisia also seems rather sedative than stimulant, but its action and that of its so-called alkaloid must vary considerably, since the latter consists at one time of hyoscine, at another of hyoscyamine. Mandragora, containing hyoscyamine and hyoscine, probably resembles hyoscyamus in its effects.

PREPARATIONS.

U. S. P.—**Belladonnæ Folia**, the leaves of Atropa Belladonna containing 0.35 per cent. of mydriatic alkaloids. Dose, 0.065 G. (1 gr.). 1 gr

EXTRACTUM BELLADONNÆ FOLIORUM (1.4 per cent. of alkaloids), 0.005–0.03 G. (1/12–1/2 gr.). 1/12-1/2 gr

TINCTURA BELLADONNÆ FOLIORUM (0.035 per cent. of alkaloids), 0.3–1 c.c. (5–15 mins.). .3-1 cc

Unguentum Belladonnæ (0.14 per cent. of alkaloids).

EMPLASTRUM BELLADONNÆ (0.4 per cent. of alkaloids).

Belladonnæ Radix, the root of Atropa Belladonna containing 0.5 per cent. of alkaloids. Dose, 0.045 G. (3/4 gr.). .75 gr

Fluidextractum Belladonnæ Radicis (0.5 per cent. of alkaloids), 0.05–0.1 c.c. (1–2 mins.). 1-2 m

LINIMENTUM BELLADONNÆ, containing camphor.

Hyoscyamus, the leaves of Hyoscyamus niger, henbane (0.08 per cent. of alkaloids). Dose, 0.25 G. (4 grs.). 4 gr

EXTRACTUM HYOSCYAMI (0.3 per cent. of alkaloids), 0.03–0.2 G. (1/2–3 grs.).

Fluidextractum Hyoscyami (0.075 per cent. of alkaloids), 0.3–1 c.c. (5–15 mins.).

TINCTURA HYOSCYAMI (0.007 per cent. of alkaloids), 1–4 c.c. (15–60 mins.). 1-4 cc

Stramonium, hyoscine the dried leaves of Datura Stramonium (0.35 per cent. of alkaloids). Dose, 0.065 G. (1 gr.). 1 gr

Extractum Stramonii (1.4 per cent. of alkaloids), 0.01 G. (1/6 gr.). [illegible] .5 cc

Fluidextractum Stramonii (0.35 per cent. of alkaloids), 0.5 c.c. (1 min.). .5 cc

Tinctura Stramonii (0.03 per cent. of alkaloids), 0.5 c.c. (8 mins.).

Unguentum Stramonii (0.14 per cent. of alkaloids).

Scopola, the dried rhizome of Scopola carniolica (0.5 per cent. of alkaloids). Dose, 0.045 G. (3/4 gr.).

Extractum Scopolæ (2 per cent. of alkaloids), 0.01 G. (1/6 gr.).

Fluidextractum Scopolæ (0.5 per cent. of alkaloids), 0.05 c.c. (1 min.).

B. P.—**Belladonnæ Folia**, the fresh leaves and branches of Atropa Belladonna.

Belladonnæ Radix, the root of Atropa Belladonna.

EXTRACTUM BELLADONNÆ ALCOHOLICUM (1 per cent. of alkaloids), 1/4–1 gr.

Extractum Belladonnæ Liquidum (3/4 per cent. of alkaloids), 1/2–1 min.

TINCTURA BELLADONNÆ (1/20 per cent. alkaloids), 5–15 mins.

LINIMENTUM BELLADONNÆ.

Unguentum Belladonnæ.

EMPLASTRUM BELLADONNÆ.

Suppositoria Belladonnæ, each containing 1/60 gr. of alkaloids.

Atropine sulphas $\frac{1}{100}$ - $\frac{1}{100}$ gr hyoscine

Hyoscyami Folia, the fresh leaves, flowers and branches of Hyoscyamus niger, henbane.

EXTRACTUM HYOSCYAMI VIRIDE, 2–8 grs.

Tinctura Hyoscyami, ½–1 fl dr.

Stramonii Folia, the dried leaves of Datura Stramonium.

Tinctura Stramonii, 5–15 mins.

Alkaloids.

ATROPINA (U. S. P., B. P.), an alkaloid ($C_{17}H_{23}NO_3$) derived from belladonna and forming white, acicular crystals, very little soluble in water, but soluble in alcohol and ether, and having a bitter taste. 0.0005–0.001 G., ½–1 mg. ($\frac{1}{200}$–$\frac{1}{100}$ gr.).

$\frac{1}{100}$ = $\frac{1}{60}$ gr

ATROPINÆ SULPHAS (U. S. P., B. P.), a white, crystalline powder, with a very bitter taste, soluble in water and alcohol. Dose, as for atropine.

Oleatum Atropinæ (U. S. P.), 2 per cent.

Unguentum Atropinæ (B. P.), 4 per cent.

Liquor Atropinæ (B. P.), 1 per cent., ½–1 min.

Lamellæ Atropinæ (B. P.), gelatin discs, each containing $\frac{1}{5000}$ gr. of atropine sulphate.

HYOSCYAMINE is not procurable in even approximately pure form and might well be dispensed with, as it offers no advantages over atropine. The sulphate and hydrobromide have been used in the same dose as atropine.

HYOSCINÆ HYDROBROMIDUM (U. S. P., B. P.), ($C_{17}H_{21}NO_4HBr,3H_2O$), the hydrobromide of hyoscine or scopolamine. It is obtained from hyoscyamus, scopola and other Solanaceæ, and forms colorless, transparent crystals with an acrid, bitter taste, and is very soluble in water, less so in alcohol. 0.0003–0.0005 G., $\frac{1}{3}$–$\frac{1}{2}$ mg. ($\frac{1}{200}$–$\frac{1}{100}$ gr.).

Scopolaminæ Hydrobromidum (U. S. P.) is identical with Hyoscine hydrobromide.

HOMATROPINÆ HYDROBROMIDUM (U. S. P., B. P.), ($C_{16}H_{21}NO_3HBr$), the hydrobromide of an alkaloid prepared from tropine by condensation with mandelic (oxytoluic) acid, a white crystalline powder soluble in 6 parts of cold water.

Lamellæ Homatropinæ (B. P.), homatropine discs, each weighing $\frac{1}{50}$ gr. and containing $\frac{1}{100}$ gr. of homatropine hydrobromide.

Therapeutic Uses.—The numerous changes produced by atropine and its congeners on the organism would indicate for them a very wide sphere of usefulness were it possible to elicit their action on one organ without affecting others and this difficulty may perhaps be overcome in the future, when the different individuals of the series have been more carefully compared, and new tropeines and other modifications of the tropine radicle are available in therapeutics.

The peripheral action of the whole series, as far as it is at present known, is so uniform that any member might be used to elicit it, but the only one that has come into general use for its peripheral effects is atropine. The purposes for which atropine is employed may be divided into groups as follows:

To Arrest or Lessen Secretions.—In rare cases of excessive *salivation* atropine has proved of service, but it is much more frequently used to lessen the *perspiration,* especially in the later stages of phthisis. For this purpose comparatively small quantities, such as ½ mg. ($\frac{1}{250}$ gr.) given by the mouth or hypodermically are generally sufficient, or the

To lessen salivation sweat, milk? Locally or hypo or mouth.
To avoid use of – in [illegible] Tx – in diagnosis of bradycardia & P irregularities. In ether anaesthesia
To dil pupil 1:1000. To paralyze accomodation 1% – absorption effects. recovers in 1 wk – pupil in 14 days.

extract or tincture of belladonna may be used instead. In local sweating, it is often applied locally in the form of an ointment, liniment, or plaster, although Tappeiner has found that it has no effect when thus employed. Atropine is also used to arrest the secretion of the *milk*, for although it has not the immediate effects on the mammary that it possesses on the salivary glands, the secretion is diminished and eventually ceases under its influence, which prevents the gland receiving any stimulation from the central nervous system. Belladonna is usually applied locally for this purpose in the form of the plaster, or less commonly as the ointment or liniment.

To Paralyze the Cardiac Inhibitory Terminations.—For this purpose a slightly larger quantity is required than is necessary to stop the secretions, and the administration of sufficient atropine to paralyze the vagus (1 mg.) therefore involves unpleasant dryness of the throat and difficulty in swallowing. In cases where slowing of the heart tends to be dangerous in itself, more especially in poisoning with certain substances to be discussed later, atropine is indicated. It may also be used for diagnostic purposes, to find if bradycardia is due to disease of the heart muscle or to inhibition. It may be repeated here that the resultant quickening is much less in old than in middle-aged people, and it is said that in many cases of old valvular lesion the administration of atropine is followed by little or no acceleration. Some forms of intermission of the pulse are due to unusual activity of the inhibitory apparatus, and these may be remedied by atropine; but this intermission possesses little importance, and seems to require no therapeutic treatment. Atropine may be used to diagnose it from the more significant forms present in organic disease of the heart. The use of atropine to paralyze the vagus terminations before the administration of an anæsthetic has been discussed already. (See page 180.)

To Paralyze the Terminations of the Motor Nerves in the Iris and Ciliary Muscles.—It is used for this purpose largely in ophthalmology as a means of diagnosis and of treatment, and the precise conditions in which it is indicated may be treated better in text-books on this subject than here. For these objects, solutions of the alkaloidal salts are generally applied to the conjunctiva, when enough of the alkaloid passes into the eye by a process of imbibition to produce marked local effects without affecting more distant organs. In order to dilate the pupil, extremely dilute solutions are used; a few drops of a solution of one in 1,000, or even of one in 10,000 are quite sufficient. Much stronger solutions are required to paralyze the accommodation, and as a general rule 1 per cent. is used. These strong solutions produce complete paralysis in 1–1½ hours, and the accommodation does not recover completely until after 5–7 days, while the pupil may not regain its normal size for 10–14 days. The application of even weaker atropine solution renders the sight imperfect for an inconveniently long period, and hyoscine and homatropine are therefore much used in its stead. The symptoms produced by a 1 per cent.

Homatropine effects off in 36 hrs, but not complete paralysis of accomodation. In glaucoma, use homatropine as can control with eserine. Rarely severe poisoning from absorption of corneal ulceration. Lead colic etc. Prevents purges griping. A purge. Spasm of ureter & bile duct. Asthma — in spray or cigarettes.

solution of homatropine pass off, or at any rate become very much less marked in the course of 36 hours. These are consequently preferable for diagnostic purposes, while atropine is rather to be used where it is desirable to produce a paralysis of longer duration, as in various inflammatory conditions of the iris or cornea. Atropine is also preferable where complete paralysis of the accommodation is necessary, as homatropine often fails to effect this. Atropine and its congeners are contraindicated where there is any suspicion of glaucoma, as, owing to their action on the intraocular pressure, they may either aggravate the disease already present or precipitate an acute attack. When dilatation of the pupil is necessary and there is reason to apprehend the results on the intraocular pressure, homatropine should be employed, as its effects can be readily controlled by eserine. Numerous cases of poisoning have arisen from the extensive use of atropine in diseased conditions of the eye. It is often asserted that it passes down with the tears through the lachrymal duct and is absorbed from the nose, throat and stomach, but as a matter of fact it may be absorbed from the conjunctiva itself. The symptoms are generally only the milder ones of atropine poisoning—dryness of the throat and slight excitement—but dangerous and even fatal poisoning has also arisen from its local application. In many cases this is due to the application of unnecessarily strong solutions to the eye, but, on the other hand, some patients seem abnormally sensitive to the action of atropine, and hyoscine, or better homatropine, ought to be preferred. In rare cases a curious inflammatory condition of the conjunctiva is set up by atropine, and this is often supposed to be due to the use of irritant preparations, but sometimes seems to follow the application of the absolutely pure alkaloid, and is apparently an idiosyncrasy; it may, perhaps, be explained by the arrest of the ordinary secretions of the lachrymal gland and conjunctiva in these cases. Sometimes discs of gelatin impregnated with atropine or homatropine sulphate (B. P.) are applied to the conjunctiva instead of solutions of the salts.

To Relax Spasm of the Intestines.—In various forms of colic atropine is of very great service in lessening pain and allowing the passage of the intestinal contents; for instance, it is preferable to morphine in lead colic, as it does not cause constipation. Hernia and volvulus are sometimes reduced by atropine injected hypodermically (3 mg. or ⅟20 gr.). It is often prescribed along with purgatives in order to lessen the griping which they produce, and has been used as a laxative in some forms of constipation with considerable success. For action on the bowel it is generally prescribed in pill form as one of the extracts of belladonna or hyoscyamus. The object of prescribing an impure preparation instead of the alkaloid is to allow of a strong local action along the intestinal wall along with a slow and imperfect absorption, as the pure alkaloidal salts are liable to be absorbed in the stomach.

To Relax Spasms of the Involuntary Muscles of Other Organs.—In the spasmodic contraction of the ureters and bile ducts due to calculi, atropine is occasionally prescribed either in the form of a pill or in

Relaxation of spasm - cures incontinence of urine in children. Anodyne - weak. C.N.S. resp. & v.m. c. & heart freed of inhibition (peripherally). In small doses in opium poisoning - but depression. Caffeine always better.

solution for internal use, or by hypodermic application. In some forms of asthma due to contraction of the bronchial muscles, atropine has been applied locally by means of a spray or given internally, and stramonium leaves are often found of benefit when made up into cigarettes and inhaled when the attack comes on; the smoke has been shown to contain small quantities of the alkaloids. Some cases of asthma are said to have been permanently cured by treatment with atropine internally. An ointment of atropine has also been applied to the cervix uteri with the hope of relaxing spasm during labor, but the results are somewhat questionable. Perhaps this action in relaxing spasmodic contractions of nervous origin may also explain the beneficial effects obtained in cases of incontinence of urine in children in which belladonna has long been the most reliable remedy.

To Lessen Pain.—Belladonna liniment, plaster and ointment have long enjoyed a considerable reputation as local anodynes, and atropine has not infrequently been injected into painful areas. This anodyne action is very weak compared with that of cocaine, however, and the preparations of atropine have been less used of late years. In some forms of gastralgia atropine has also been suggested.

The Effects on the Central Nervous System of the members of this group are very different, and the purposes for which they are used are diametrically opposed. Atropine is used as a stimulant in various conditions of depression of the brain and medulla oblongata. Thus, in collapse its hypodermic injection may be of use to stimulate the respiratory and vaso-constrictor centres, and at the same time to free the heart from excessive inhibition. In dangerous poisoning from narcotic and hypnotic drugs, more especially in opium poisoning, atropine has been largely used. A long and weary dispute as to the value of atropine in those cases has been carried on, for the history of which the reader is referred to the recent paper by Bashford. The results indicate that atropine is useful in morphine poisoning through stimulating the respiratory centre, which is the danger point. But it must be employed in small quantities (1.5 mg. or 1/40 gr.), as large ?
doses, such as have frequently been advised, tend to depress the central nervous system and thus to aid rather than to antagonize the action of morphine on the respiration. It may be questioned whether in any case atropine may not be replaced by caffeine with advantage. The former stimulates the medullary centres, but subsequently paralyzes them, while caffeine, even in comparatively large quantities, does not seem to have a depressant action in man.

Atropine at one time had some reputation in the treatment of epilepsy. It has been shown both clinically and experimentally that this reputation was undeserved, the number of attacks and their violence being rather increased than diminished by its exhibition; the belief in its powers arose from the use of impure preparations containing hyoscine.

In some spasmodic diseases, such as whooping-cough, belladonna preparations have long enjoyed a wide reputation; a possible expla-

Hyoscine – insanity – sound. No use in insomnia from pain. Normal sleep. Chloral = deep. Indicated in much motor activity & some tremors 1/6 morph + 1/200 hyoscine & much less ether necessary. See Richard's notes. Symptomatic treatment for Poisoning – ether for delirium. Not morph (resp)

In depression stage caffeine & artificial resp. Pilocarpine for local effect.

nation is that the hyoscine may allay the spasms by reducing the excitability of the respiratory centre.

Hyoscine or scopolamine has been used as a narcotic to depress the central nervous system; it is of great efficacy in insanity, producing sound and refreshing sleep, but is of less value in controlling the excitement during the day, and may in fact increase it. Hyoscine is also used with benefit in various forms of tremor of central origin, and is said to lessen sexual excitement. Its hypnotic action does not seem to be of the same nature as that of opium, for in sleeplessness produced by pain it is of comparatively little value, and it has no power to relieve pain itself. It differs from chloral in not inducing deep sleep, for patients under the influence of hyoscine can always be aroused and are much less confused than after chloral. The special indications for hyoscine seem to be sleeplessness due to abnormal activity of the motor areas and some forms of tremor.

Comparatively recently morphine and hyoscine have been injected as a preliminary to surgical operations, but as a general rule the narcosis induced is insufficient. As a preliminary to the use of ether the procedure seems to be of value, as much less of the anæsthetic is required; 10 mgs. (1/6 gr.) of morphine and 0.3 mg. (1/200 gr.) of hyoscine are injected 1½ hours before the operation.

Poisoning.—In cases of poisoning with belladonna and its allies the treatment is purely symptomatic. In the excitement stage sedatives may be used; perhaps chloroform and ether are best, as their effects are more transient than the others. Morphine has been advised, but its action on the respiratory centre renders its use dangerous, as in severe atropine poisoning the stimulation soon passes into depression, and the effects of the poison and its so-called antidote therefore supplement each other. Chloroform and ether, on the other hand, may be used to control the spasms and then stopped when these pass off. In the depression stage caffeine may be used, and eventually artificial respiration. Pilocarpine is of course useless, as it does not antagonize atropine in the brain, which is the point of danger.

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Compare also the Literature of pilocarpine and. muscarine, nicotine and physostigmine.

Agaricin.

White Agaric (Agaricus albus, Boletus Laricis), a fungus growing on the European larch tree, was formerly a purgative and antihydrotic of some repute. Its use to lessen the perspiration (antihydrotic) has been revived of late years, or rather a preparation known as agaricin and containing the active principle has been introduced into therapeutics. Agaric or Agaricinic acid, the active constituent, belongs to the malic acid series and has the formula $C_{14}H_{27}(OH)(COOH)_2$.

Action.—Both the acid and its sodium salt irritate the mucous membranes and wounded surfaces, and cause inflammation and even suppuration when injected subcutaneously. Large quantities irritate the stomach and intestine and cause vomiting and purging, but these are more liable to arise from the impure agaricin owing to its containing resinous acids. Injected into the frog, agaric acid paralyzes the central nervous system, weakens the heart and stops the secretion of the skin glands. In mammals the intravenous injection of agaric acid is followed by depression, weakness, dyspnœa and death. The medulla oblongata is first stimulated and then paralyzed, as is shown by the blood-pressure first rising and then falling to zero, while the heart is primarily slowed by inhibitory action and later regains its rhythm, eventually to fail after the arrest of the breathing. Animals can only be poisoned with difficulty by the subcutaneous injection of agaricin, and no general symptoms are elicited when it is administered by the mouth.

The most interesting feature of the action of agaric salts is the arrest of the sweat secretion, which is caused by peripheral action, for stimulation of the nerves of the cat's foot fails to elicit perspiration after its ingestion. It thus acts on the same peripheral mechanism as atropine in all probability, that is, on the terminations of the secretory nerves, but differs from atropine in acting only in the sweat glands, for the saliva, tears and other secretions are not hindered by it, and may, in fact, be increased by its causing nausea. It is also devoid of action on the nerve terminations in the heart and pupil. Atropine acts much more powerfully than agaric acid, at least twenty times as much of the latter being required to arrest the sweat secretion.

Uses.—Agaricin is used in the night sweats of phthisis and other similar conditions and is generally given in pill form in doses of 5–60

Camphor + O = Camphoric acid – less [illegible] [illegible] than camphor [illegible] depresses sensory fibres to sweat glands (but does not dil pupil or dry mouth) (as no dry mouth or dimming of sight) used in night sweats of phthisis

mgs. ($\frac{1}{12}$–1 gr.). The commercial agaricin often contains a large percentage of impurities and has to be given in larger quantities, but the treatment ought to be begun with small doses. Tolerance is said to be acquired after some time, and the dose has then to be increased. The best results are got when the pills are taken 5–6 hours before retiring, as the acid is only slowly absorbed. If agaricin causes intestinal irritation and diarrhœa it may be given with opium, but as in phthisis all irritation of the bowel is to be avoided, the remedy ought perhaps to be stopped when any such disturbance arises.

Other antihydrotics are atropine and camphoric acid. Agaricin is preferable to atropine, because the latter tends to cause dryness of the throat and other symptoms when it is given for some time even in very small doses.

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Camphoric Acid.

Camphoric acid is derived from camphor by oxidation and possesses the formula $C_8H_{14}(COOH)_2$. In very large quantities it is said to elicit symptoms from stimulation of the central nervous system resembling those observed in camphor poisoning, but it acts much less powerfully than camphor and in fact is stated by some authors to be devoid of toxic effects. On the other hand, it acts on the terminations of the secretory fibres to the sweat glands in the same way as atropine, for pilocarpine fails to induce perspiration after its administration. Its action seems to be confined to these glands for it does not arrest salivation nor dilate the pupil.

Acidum camphoricum (U. S. P.), $H_2C_{10}H_{14}O_4$, an acid obtained by the oxidation of camphor, forms colorless crystals slightly soluble in water. Dose 1–2 G. (15–30 grs.). 1-2G

Uses.—It has been used to lessen the night sweats of phthisis and other similar conditions, and is given for this purpose in powders of 15–30 grs. It is slowly absorbed and should therefore be given an hour or two before bedtime. It possesses the advantage over atropine of not causing dryness of the throat and indistinct vision, and on the other hand does not tend to disturb the digestion as agaricin often does. But it is much less certain in its effects than atropine, and according to some authorities is of comparatively little value.

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XIV. COCAINE.

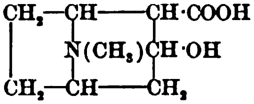
Cocaine is a comparatively recent addition to therapeutics, although the coca plant has been in use in South America for centuries. It is indigenous there, but has been introduced into India, Ceylon and

CNS. stim. – excitement, confusion – small dose maybe languor – pulse up, resp up. pupil dil. headache & dryness of throat. Reflexes sensation tremors sometimes vomiting. Then convulsions & collapse.

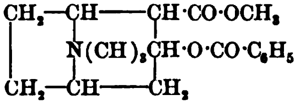
Java. The leaves of the coca grown in Peru and Bolivia contain cocaine along with small quantities of other alkaloids, but the India coca and still more the Java leaves contain a smaller proportion of cocaine and a larger amount of the less known alkaloids.

Cocaine, like atropine, is readily decomposed into several constituents. On heating it with water, methyl alcohol is thrown off, leaving *Benzoyl-ecgonine,* which may be further broken up into benzoic acid and *Ecgonine,* a pyridine derivative.

Ecgonine.



Cocaine.



Cocaine is capable of being changed in several different parts of its structure. Thus ethyl or propyl may be substituted for the methyl group, the benzoyl radicle may be replaced by various others, such as cinnamyl, and so on. Many artificial cocaines have been formed in this way, and several of these have since been found in the cultivated plant, as for example *Cinnamyl-cocaine,* in which cinnamyl occupies the position of benzoyl in the above formula. Various other alkaloids, such as *Cocamine, Isococamine, Homococamine* and *Homoisococamine* are also present; all of these contain the ecgonine molecule in combination with various acids, and cocaine may be formed from all of them by isolating the ecgonine and combining it with benzoic acid and methyl. These alkaloids are present in the plant in very small quantities compared with cocaine and have not been used therapeutically. Another alkaloid which has been found in the Java coca is *Tropacocaine,* which is a combination of benzoic acid and a base ($C_8H_{15}NO$). It will be observed that the formula of ecgonine resembles very closely that of tropine, each containing the same nucleus, but differing slightly in the radicles attached to it.

The most important effects of cocaine are those on the central nervous system and on the sensory nerves.

Symptoms.—The symptoms of cocaine poisoning in man vary a good deal in different individuals. In most cases small quantities produce some excitement, pleasurable or disagreeable. The patient is generally restless and more garrulous than in ordinary life, often somewhat anxious and confused. But very often a small dose is followed by a calm, languorous state, somewhat resembling that induced by small quantities of morphine, but differing from it in there being less tendency to sleep. The pulse is accelerated, the respiration is quick and deep, the pupil generally dilated, and headache and dryness of the throat are often complained of. The reflexes may be found somewhat more easily excited than usual and tremors or slight convulsive movements often occur. Later, powerful tonic or clonic convulsions supervene, the heart becomes extremely accelerated, the breathing becomes rapid and dyspnœic and may be finally arrested during a convulsion. In other cases the convulsive seizures are almost entirely absent and fainting and collapse occur. The skin is cyanotic and cold, the heart slow and weak; the respiration is very much depressed and death follows from its gradual cessation. Vomiting is occasionally seen at an early stage, but is not by any means common.

Nervous: Excitement - movements at first coördinated. More work, less fatigue, well done, same for brain. With larger doses stim. of cord, then muscular restlessness convulsions

In the dog, cat and rabbit the symptoms are invariably those of stimulation of the central nervous system. Soon after the injection the animal shows symptoms of great restlessness and excitement; it seems unable to keep still, the dog at first showing all the signs of affection and excitement which he displays on ordinary occasions on being unchained or taken for a walk, but afterwards running continually in a circle and paying but little heed to anything around him. Still later regular convulsions occur, and these are at first clonic, but may afterwards become tonic, and then resemble those seen in strychnine poisoning. Even before the convulsions appear the animal seems partially unconscious, and in the intervals between them he lies in an apathetic state, which soon deepens to coma and death from asphyxia.

In the frog a certain amount of stimulation of the central nervous system is often displayed after small doses—increased movement, exaggerated reflex and occasionally convulsions—but these soon pass into depression and eventually total paralysis of the central nervous system, while the peripheral nerves still maintain their functions.

General Action.—Many of these symptoms point to a stimulant action on the **Central Nervous System**, resembling closely that seen in atropine poisoning. Thus the garrulity which is so often produced by cocaine indicates an increased activity of the cerebrum, and the increased movement in the lower animals distinctly points to an affection of this part of the brain, for the movements are perfectly coördinated, and, in fact, in the early stages resemble exactly those performed by the normal animal in a condition of excitement. Further evidence of the action of cocaine on the cerebrum is offered by its effects on muscular work. The natives of Peru and Bolivia have used it for centuries to increase their endurance of fatigue. The bearers of the Andes, for example, march for hours and days with very little rest or food when they are supplied with coca leaves to chew. The effects of cocaine on the muscular power and on fatigue have been investigated also by means of the ergograph and dynamometer, and all observers are at one in asserting that much more work can be done after cocaine than before it, and that it has a surprising potency in removing fatigue. As regards mental work, its effects are less known, but on the analogy of caffeine it may be supposed to increase the mental powers also when taken in small quantities. Some travellers in South America relate marvellous tales of its producing feelings of the highest bliss and power, but these have not been confirmed by experience in the action of cocaine in less romantic regions of the globe. Cocaine in small quantities, then, increases the higher functions of the cerebrum, while in somewhat larger doses the stimulant effect spreads to the lower areas and produces a very great increase in movement, accompanied, it would seem, by a depression of the consciousness. At the same time, the coördinating or balancing powers seem affected, so that the animal generally moves in a circle, the symptoms resembling the forced movements often seen in affections of the cerebellum.

The motor areas of the cerebrum have been found to be more easily descending stimulation, then descending depression – both including medulla, often overlap. Resp at first up then down. Even Cheyne-Stokes. Heart possibly directly stim or accelerator fibres stim., & vm stim + vessels directly constricted = high b.p. later dilates vessels so b.p. low

stimulated by the electric shock when cocaine is injected, though when it is painted on the surface of the brain it lowers the irritability, owing to its being present in too great concentration. Still larger quantities induce convulsions, which are not of spinal origin, but point rather to action on some undetermined part of the hind brain. At an early stage the medulla oblongata is affected, as is shown by the quickened respiration, and the exaggerated reflexes indicate stimulation of the spinal cord, which may be so great after very large doses as to cause convulsions like those produced by strychnine. The action of cocaine on the central nervous system is primarily a descending stimulation, the cerebrum being first affected, then the hind brain and medulla oblongata, and last of all the spinal cord. Perhaps it might be better expressed by saying that after small quantities the chief symptoms arise from the cerebrum, but as the dose is increased those from the lower parts of the central axis tend to become more prominent. After the stimulation there succeeds depression, which follows the stimulation downwards, affecting first the cerebrum and then the lower divisions. The two stages are not definitely divided, however, one part of the cerebrum often showing distinct depression, while another is still in a condition of excessive activity. In some cases, especially in man, the stage of excitement may be very short or apparently absent and the whole course of the symptoms then points to medullary depression.

The **Respiration** after cocaine is much accelerated, owing to central stimulation. At first the depth of the movement is not changed, but as the acceleration progresses the air inspired with each breath gradually becomes less. During the convulsions the respiration is irregular or ceases, but it recovers again in the intervals, until after a very violent paroxysm it fails to be reinstated. In other cases the breathing becomes slower and weaker after a time, and eventually stops from paralysis of the centre. Periodic respiration is frequently seen, of the form generally known as Cheyne-Stokes'. (See Morphine, page 218.)

The **Circulation** is altered by cocaine, owing to its action on the heart and on the vessels. The heart is much accelerated in mammals, while in the amphibians this is less often observed. The quickening has been ascribed to paralysis of the inhibitory terminations, but this seems not to be the case, for stimulation of the vagus slows the heart even late in the poisoning. The heart is accelerated, then, either by direct action on the muscle or by stimulation of the accelerator mechanism. It is often slow before death, but apparently not invariably, and this is probably due to direct action on the muscle. In the frog's heart the inhibitory apparatus is paralyzed, the ganglia being affected in the same way as by coniine and other drugs.

The vessels are much contracted in the earlier stages of poisoning, and this, together with the increased rate of the heart, leads to a very considerable rise in the blood-pressure. The constriction of the vessels seems partly due to stimulation of the vaso-constrictor centre, for

Gi. pallor + peristalsis. large dose – dil of vessels + paralysis of [illegible]. Vessel changes determine urine. Central action: temp up. ~~Ex~~ Metabolism up, tho hunger sensation decreased. Liver degeneration. 95% burned. Rest → kidney

section of the splanchnic nerves leads to an immediate fall in the arterial tension. But cocaine also exercises a direct action on the vessel walls, for its local application leads to constriction of the vessels and blanching of the mucous membranes. It has not been determined as yet how far this direct action on the vessel walls affects the blood-pressure when cocaine is absorbed or when it is injected intravenously. The blood-pressure subsequently falls, apparently from peripheral action, if Anrep's assertion that stimulation of the splanchnic then produces no further rise of pressure be correct.

The effects on the peripheral **Nerves and Muscles** are disputed, for Mosso states that small quantities increase the strength of the muscular contractions on electrical stimulation both in man and animals, while others have failed to obtain any such effect.

After the injection of cocaine, Anrep observed marked pallor of the **Intestine** and powerful peristalsis, while very large doses caused dilatation of the mesenteric vessels and lessened the movements of the bowel probably through paralyzing the local nervous mechanism.

The **Urine** is sometimes said to be increased by cocaine, while in other instances its injection has been followed by total anuria lasting for several hours. This suggests that the action is not a direct one on the kidney, but is caused merely through the changes in the calibre of the vessels.

The other **Secretions** seem rather decreased than augmented, but no very marked effects are produced on them.

The **Temperature** generally rises in cases of poisoning, sometimes as much as 3–5° C., from increased heat formation caused by cerebral action. Langlois and Richet observed that the higher the temperature of the animal the more easily were convulsions produced by cocaine and the more severe their type.

It used to be supposed that cocaine retarded the **Tissue Change** and that less food was required when it was supplied. This was based on the statement of the endurance of the natives of South America when they were allowed to chew coca leaves, and on the discovery that the leaves also allay hunger to some degree. But the increase in the working power is due to the effects on the central nervous system, while the craving for food is probably lessened owing to the cocaine inducing numbness of the sensory nerves of the stomach through its local action.

A curious effect of cocaine, noted by Ehrlich in mice, is a widespread destruction of the hepatic cells, which become infiltrated with fat and often undergo necrosis.

Some cocaine is **Excreted** by the kidney in the dog when it is absorbed into the blood, but 95 per cent. of that ingested is destroyed in the tissues, and this is the fate of all of it in the rabbit, in which this oxidation proceeds very rapidly. It is unknown whether it is oxidized in man, who is much more susceptible to its action than these animals.

Local Action.—Cocaine applied locally in most parts of the body produces a loss of sensation through its paralyzing the **Terminations of some of the Sensory Nerves,** particularly those conveying impressions

to endings terminations of sensory nerves. loss of pain + touch + bitter taste. Slow penetration thru horny epidermis. Hypo - numb + painless - acts on endings + fibres + shuts off sensations of parts supplied. With injection to cord motor function unimpaired. So selective. → in small doses
No action after absorption (not conc)

of pain and touch. The exact researches of Kiesow show that heat and cold are recognized as readily as in the unaffected parts of the body. Cocaine applied to the tongue removes the taste of bitter substances, while sweet and acid fluids lose their taste only partially, and salt is recognized as easily as usual.[1] A solution applied to the nasal mucous membrane paralyzes the sense of smell entirely. The anæsthesia or insensibility to pain and touch may be induced in any of the mucous membranes that can be reached by cocaine in sufficient concentration, pharynx, larynx, œsophagus, stomach, nose, eye, urethra, bladder, vagina and rectum. Applied to the unbroken skin its effects are less marked, as it penetrates but slowly through the horny epidermis; but when the epidermis is removed by abrasions or by skin disease, the cutaneous organs of sensation are acted on in the same way as those of the mucous membranes. The deeper sensory terminations can also be acted on by hypodermic injection, which causes a feeling of numbness and the relief of pain in the part. Hypodermic injection reaches not only the nerve terminations of the subcutaneous tissues, but also the finer nerve bundles, and these too are rendered insensible as far as the solution extends to them. The part may therefore be cut into or be subjected to other surgical treatment without pain, as long as the knife does not pass beyond the area to which the drug has penetrated, and numbers of grave surgical operations have been performed under the local anæsthesia produced by cocaine. Injected into the neighborhood of a nerve trunk, cocaine penetrates into the fibres and induces anæsthesia of the organs supplied by the nerve, and injected into the spinal canal it causes anæsthesia over large areas of the body, sometimes over almost the whole body; this is probably due to its acting on the posterior roots of the cord. It must be noted that the anæsthesia is only produced by the local application of the drug. The internal administration only leads to a partial loss of sensation in the throat and stomach, and no anæsthesia is induced by its action after it reaches the blood vessels. The reason for this evidently is that in order to paralyze the sensory fibres and terminations a considerable amount of the drug is required, but much less is necessary to paralyze the central nervous system. Even in the frog the sensory terminations are not fully paralyzed until all symptoms of reflex excitability have disappeared and total paralysis has supervened.

Cocaine applied to a nerve trunk proves to have a distinct selective action, for the sensory fibres fail to conduct sensory impressions, while motor impulses pass through the fibres without difficulty. Similarly, when it is injected into the spinal canal, complete loss of sensation in the lower part of the body follows, but the movements are almost unimpaired. This selection is only relative, for larger quantities

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[1] A curious contrast is presented in this respect by gymnemic acid, which is obtained from the Gymnema silvestre, and which removes the sensation of sweetness, while "bitter" is less affected and "acid" and "salt" are recognized as readily as usual. Gymnemic acid does not affect any other sense organs, as far as is known, and is, in fact, devoid of interest, except as regards its effect on taste.

Locally constricts vessels pallor · With absorption, sensation returns
Eye: const. of vessels, anaesthesia, dilation of pupil, but retaining power to accomodate itself to light

paralyze the motor nerve fibres also; no explanation has been given for this difference in the reaction of the two sets of fibres.

When cocaine is applied locally to a mucous membrane it produces, besides a loss of sensation, a feeling of constriction and a distinct pallor and contraction of the vessels, which point to a local action on the vessel walls.

The anæsthesia produced by cocaine is comparatively short, but varies with the strength of the solution applied and with the vascularity of the part; as soon as the cocaine is absorbed, the local action disappears and sensation returns.

FIG. 29.

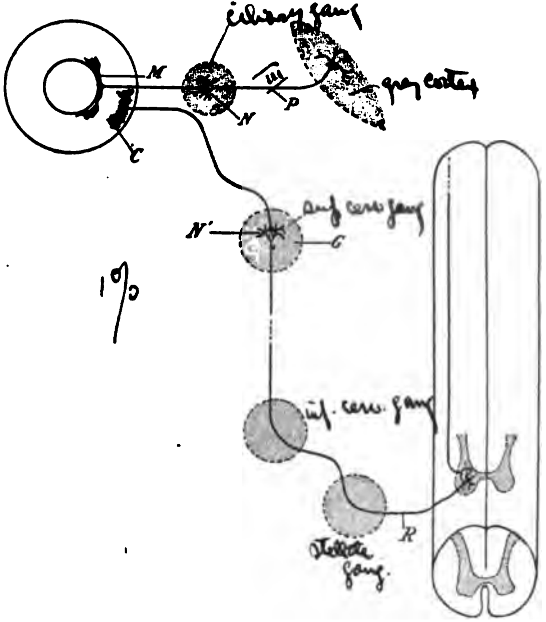

Diagram of the innervation of the iris. *P*, a fibre of the motor oculi passing from the brain to the ciliary ganglion *N*, in which it terminates around a nerve cell, which sends an axis cylinder to terminate, *M*, in the circular fibres of the iris. *R*, a spinal nerve fibre issuing from the lower cervical cord, running through the stellate and inferior cervical ganglia and terminating around a ganglion cell in the superior cervical ganglion, *G*. The axis cylinder from this nerve cell runs to the iris (passing the ciliary ganglion) and terminates in fibrils *C*, on the radiating fibres. *C* is the point which cocaine stimulates and the resultant contraction of the muscle fibres causes dilatation of the pupil, but when strong impulses descend to *M*, as happens when the eye is exposed to bright light, the circular muscle overcomes the weaker radiating fibres, and the pupil is contracted. In the same way strong stimulation of *M* by muscarine overcomes the stimulation of *C* by cocaine, while, on the other hand, when *M* is paralyzed by atropine and the circular fibres are thus thrown out of action, the radiating muscles are unopposed, and cocaine causes a greater dilatation than in the normal eye.

Cocaine is applied to the **Eye** more frequently than to any other part. It produces local anæsthesia here, along with contraction of the conjunctival vessels, and this is followed by dilatation of the pupil and often by partial loss of the power of accommodation. The dilatation of the pupil is much less than that produced by atropine, and differs from it in several respects. Thus, the light-reflex is preserved, the

Dil of pupil by stim of dil sympathetic fibres. Exopthalmos + intraocular tension reduced - sympathetic action after absorption. V cons. + pupil dil may be effected locally. General protoplasm poison in solution - depression paralysis death - May intensify Corneal ulceration etc.

pupil contracting in bright light and dilating further in the dark; a number of drugs which have little or no effect after atropine, contract the cocainized pupil (pilocarpine, muscarine, physostigmine), while atropine dilates it still further, and cocaine produces some dilatation after the full atropine action has been elicited. It is evident, then, that the two drugs produce dilatation by acting on different mechanisms, and although the way in which cocaine dilates the pupil has been a matter of dispute, the great majority of investigators now hold that it stimulates the terminations of the dilator fibres. (Fig. 29.) The motor oculi is not involved in its effects, unless very large quantities are applied, when its terminations may be depressed in the same way as by atropine (Schultz). A strong argument in favor of the view given above has been found in the observation that when the dilator nerves degenerate, owing to removal of the superior cervical ganglion, cocaine fails to cause dilatation of the pupil.

Several other symptoms are produced by the local application of cocaine to the eye, at any rate in some instances. Thus, the iris vessels are sometimes much constricted, the eye is more widely open than usual, so that the white sclerotic is seen above and below the iris, the whole eyeball is pushed forward (exophthalmos), and the intraocular tension is said to be considerably reduced. All of these features are produced only after cocaine has been applied in considerable quantity and for some time, and may be due, at any rate in part, to its absorption. They may all be observed in the unpoisoned animal when the cervical sympathetic trunk is stimulated, and therefore seem to indicate a special action of cocaine on the centres or terminations of this nerve. All of these symptoms, except the anæsthesia and the pallor of the conjunctiva and iris, are produced by the injection of cocaine as well as by its local application, but in this case are prevented by previous section of the cervical sympathetic. Cocaine does not produce any dilatation of the pupil in birds.

Cocaine brought into immediate contact with nerve terminations paralyzes them, but this is true for so many other forms of living matter that it may be regarded as a **General Protoplasm Poison.** Thus muscles, nerves and nerve ends cease to contract or to conduct stimuli when they are exposed to even very dilute solutions of cocaine; the ciliated epithelial cells, leucocytes and spermatozoa become motionless; the cortical nerve cells lose their excitability, and many of the invertebrates are killed by even a short exposure to cocaine. The movements of protoplasm in plants are also retarded or entirely suppressed by this poison, and the process of putrefaction is delayed considerably. In some cases, notably in the higher invertebrates, the final depression is preceded by a stage of increased movement, and it is said that the irritability of nerve is also augmented at first. In other instances, however, cocaine induces only depression and paralysis.

Other examples of this destructive action are also seen in the therapeutic use of cocaine, for the cornea is often rendered somewhat

Cocainae hydrochloridum $\frac{1}{6}$-$\frac{1}{2}$ gr- sol. H_2O & CH_3CH_2OH
Caffeine better in depressed conditions. Vinum as tonic forms habit
Anaesthetic locally & g-mydriatic. Over vessels-lessening of [illegible]. Complete anaesthesia 4%
7 min for 30 Lesser pains 1-2%

cloudy from its application, and its subcutaneous injection is sometimes followed by necrosis. Victims of the cocaine habit often show numerous scars on the arms and legs from this local gangrene, although this is probably often due to unsterilized syringes rather than to the solution.

Most of the other natural alkaloids resemble cocaine in many points of their action, as far as they have been investigated, but some of the artificial compounds present divergences from the general type. Thus a number of them do not produce anæsthesia, and some of them depart entirely from the typical cocaine action.

Cocamine is often said to be a cardiac poison, but its action on the heart seems to resemble in general that of cocaine. It has, however, a much more intense action on muscular tissue, which it, like caffeine, throws into rigor mortis. Its anæsthetic power is very small. Some authorities regard the muscular action of caffeine as an important factor in its preventing fatigue, and the presence of cocamine in the coca leaves might be used to explain the similar effects induced by these, but the quantity is probably too small to have any noticeable action.

Benzoylecgonine is a comparatively weak body, which produces symptoms resembling caffeine—increased reflex excitability, muscular stiffness and rigor—and *ecgonine* is still less active, but elicits in frogs similar effects.

PREPARATIONS.

Coca (U. S. P.), the dried leaves of Erythroxylon coca, containing at least one-half per cent. of alkaloids. Dose, 2 G. (30 grs.).

COCAINA (U. S. P., B. P.), an alkaloid ($C_{17}H_{21}NO_4$) obtained from the leaves of Erythroxylon coca and its varieties, forming colorless crystals with a bitter taste followed by numbness; insoluble in water, ~~soluble in alcohol~~.

COCAINÆ HYDROCHLORIDUM (U. S. P., B. P.) ($C_{17}H_{21}NO_4HCl$), colorless crystals, ~~very soluble in water~~ and alcohol; watery solutions cannot be boiled as the alkaloid ~~tends to decompose~~, 0.01–0.03 G. (⅙–½ gr.). $\frac{1}{6}$-$\frac{1}{2}$ gr

Lamellæ Cocainæ (B. P.), each contains $\frac{1}{50}$ gr. ~~of the~~ hydrochloride.

Injectio Cocainæ Hypodermica (B. P.), 10 per cent., 2–5 mins. 2-5 m

Unguentum Cocainæ (B. P.), 4 per cent.

Oleatum Cocainæ (U. S. P.), 5 per cent.

Trochisci Krameriæ et Cocainæ (B. P.), each contains $\frac{1}{20}$ gr. of the hydrochloride.

The Therapeutic Uses of cocaine are almost all dependent on its anæsthetic action. It has been suggested as a brain stimulant in various conditions of mental depression, but has not been widely used for this purpose, which is better served by the less dangerous caffeine. A wine containing coca extract is often used in domestic medicine as a "general tonic," and has repeatedly given rise to the cocaine habit.

Its anæsthetic properties render it extremely important. In ophthalmic surgery it is used very largely both during operations and to alleviate pain, and occasionally to constrict the vessels of the iris in inflammatory conditions. For complete anæsthesia a 4 per cent. solution may be employed, while to allay pain one of 1–2 per cent. is all that is necessary. The anæsthesia is of short duration, generally setting in after 5–7 minutes and passing off 20–30 minutes after the application of the drug. Occasionally cocaine, especially in strong solution, produces a certain amount of opacity of the cornea, and it is

Lessens healing power of tissues. Dil of pupil less marked than atropine & [illegible]
reacts to light so of little use in examinations. But less dangerous in glaucoma
& a few drops of physostigmine = removal of dil. Pharynx etc surgery. vess + less
pain 4.-10%. Hay fever. Urethra rectum etc anaesthetic. Checks vomiting from
irritation.

stated that wounds heal less readily, and irritant antiseptics are more dangerous with cocaine than without it. This may sometimes be due to the use of impure cocaine, but it may be noted that cocaine is a protoplasm poison, and may therefore lessen the resistance of the tissues with which it comes in contact. The usual explanation given that cocaine paralyzes sensation in the cornea, and thus prevents the reflex winking which removes foreign bodies from the surface and keeps the eye moist, is obviously insufficient, as the anæsthesia is of but short duration. The dilatation of the pupil produced by cocaine is much less complete than that under atropine, and can only be taken advantage of in diagnosis by using very dim light, as the pupil contracts in bright light almost to its normal size. On the other hand cocaine is much less injurious in glaucoma and the dilatation can be removed at once by the instillation of a few drops of physostigmine.

In the nose, throat and larynx, cocaine is used in a solution of 4 per cent., sometimes 10–20 per cent., and anæsthesia is obtained with greater difficulty than in the eye, but the local contraction of the vessels is often of great service. Cocaine is used largely in operative procedure here and also in the treatment of irritable conditions of the respiratory passages, such as hay fever. In the urethra, rectum and vagina, cocaine may also be used either as an anæsthetic or to relieve pain temporarily. It is sometimes of service in painful or itching skin diseases, but care must be taken not to apply it to large broken surfaces, otherwise symptoms of poisoning may follow. The local action on the stomach is often valuable in checking vomiting due to gastric irritation.

For many years after its introduction as a local anæsthetic in 1884, its use was practically limited to minor operations in the nose and throat and to ophthalmic surgery, few general surgeons venturing on its application in other fields. Within the last few years, however, its use has undergone a wide extension, so that almost all the major surgical operations have been performed under it, and local anæsthesia by means of cocaine ~~or eucaine~~ has now become a rival of ether and chloroform. Occasionally partial local anæsthesia is combined with the administration of small quantities of chloroform or ether, which are insufficient to produce complete unconsciousness, but cause a numbing of the sensation, which, together with the local action, permits of a painless operation. At first strong solutions were injected to prepare the way for the knife, each step forward in the operation being preceded by an injection of cocaine to induce anæsthesia of the layer of tissue to be incised. But this method, which has been used chiefly by Reclus, required dangerous quantities of the drug, and is now scarcely used except for minor operations in which a single injection is sufficient. A more satisfactory method of local anæsthesia for operative purposes has been introduced by Schleich under the name of *infiltration anæsthesia*. A large quantity, sometimes as much as 200 c.c. of a solution containing 0.01 per cent.[1] of

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[1] Some operators use a 0.1 per cent. solution and inject less.

Schleich - infiltration anaesthesia - .01% sol + .8% NaCl (unfiltered) - even 200 cc. Or .1% & less. Oedema anaesthesia. Regional anaesthesia - near nerve
3 drops 1:1000 adrenalin for ever 50 cc. cocaine = vasoconst & less absorption.
Subarachnoid 1 cc of 2% coc HCl (1/5 gr) after withdrawal of fluid - motion retained so

not complete relaxation. Vomiting headache. Abdomen + legs = loss of sensation for 30 min.
action post. roots

cocaine and 0.8 per cent. of sodium chloride is allowed to permeate the tissues through a fine hypodermic needle. Only very slight pressure is required and the whole of the surrounding structures become swollen and œdematous and can be cut into without pain. Much of the fluid escapes through the incisions and no symptoms of poisoning arise. Schleich attributed the anæsthesia partly to the pressure exerted by the solution and partly to the imbibition, but later investigators have found it to be dependent on the cocaine alone.[1] Another method (*regional anæsthesia*) is the injection of cocaine into the immediate neighborhood of the nerve supplying the part to be operated on. Complete local anæsthesia is obtained, and shock is less liable to occur than when general anæsthesia is induced (Crile). This method has been used extensively in operations on the foot and hand, for which it is admirably suited; it is difficult to adapt it to other parts of the body. The local action in both infiltration and regional anæsthesia may be augmented and the danger of general poisoning lessened by retarding the circulation in the part to be operated on. This may be done by applying an Esmarch bandage above it when a limb is involved, or by the application of cold by means of ethyl chloride; but the best results are obtained by using a 1 per mille solution of adrenaline along with cocaine. This contracts the vessels and arrests the circulation locally, and the cocaine thus remains longer unabsorbed. Braun recommends 3 drops of 1 per mille adrenaline solution to 50 c.c. of cocaine solution for infiltration.

After it was found that the nerve impulses from the periphery to the central nervous system could be blocked by the injection of cocaine into the peripheral nerves, the next step was to obstruct them higher in their course by applying it to the spinal roots (*subarachnoid anæsthesia*). The first to attempt this was Corning of New York, but the development of the procedure is due to Bier and Tuffier. A long hollow needle is passed into the spinal canal between the laminæ of the lumbar vertebræ and 1 c.c. of a 2 per cent. solution of cocaine hydrochlorate is injected after the withdrawal of an equivalent amount of cerebrospinal fluid. The actual amount of cocaine injected is thus 0.02 G. (⅓ gr.). Within a few minutes numbness begins, generally in the feet at first, but sometimes in the lower part of the trunk; it spreads upwards rapidly until sensibility to pain is lost everywhere below the diaphragm and sometimes in the thorax; in some cases even the head has been found anæsthetized. The sensations induced by warmth and cold are less quickly affected, touch is preserved to some extent and the limbs can be moved readily, though the movements are carried out more slowly than usual; the consciousness is unimpaired. This condition lasts from half an hour to an hour and then sensation returns gradually. In the beginning of the action some muscular twitching is often seen, and the muscles are never relaxed as they are under chloroform or ether. Vomiting occurs in a certain proportion

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[1] Heinze showed that the morphine contained in Schleich's original fluid was superfluous.

Schleich — never over 1/3 gr. Stop to inject another large
Cocainism — Gi. disturbances — appetite, emaciation, salivation. Convulsions,
hallucinations, insanity, delirium. Withdraw drug & sent to sanatorium.

of cases either during or after the operation, and persistent headache is often present. The cocaine is believed to act on the posterior nerve roots and not on the cord itself. The cerebrospinal fluid has been found to contain a large number of polynuclear leucocytes after the injection and resumes its normal limpid character only after several days. This method of anæsthesia has been used in a large number of operations, some of them of the gravest nature; it has also been substituted for general anæsthesia in labor.

Of these methods, Schleich's infiltration has been most widely adopted and is admirably suited for minor operations. It is the safest method available for most of these, for the amount of cocaine injected ought not to be sufficient to induce poisonous symptoms, and should never exceed 20 mg. (⅓ gr.) and much of this escapes by the incision. It requires some experience to induce complete insensibility to pain by this method and the operation has to be interrupted at intervals to permit of further injections. Some headache and nausea are occasional sequelæ. When general anæsthesia is contraindicated, infiltration may be adopted in major operations, while on the other hand it is often contraindicated in minor operations where there is any possibility of complications, or where the anxiety and nervousness of the patient are likely to interfere with the proceedings. Subarachnoid or intraspinal cocainization is still on trial, and while it has been enthusiastically praised by some of its sponsors, it has in general been regarded as a hazardous method. Numerous fatalities have resulted from it, and headache and nausea very often persist for many hours after the operation. It seems probable that it will in the future attract less attention than it has recently, and will be regarded as a last resort to be used when special circumstances contraindicate the general anæsthetics and operation is imperative.

Cocaine Habit.—Since the introduction of cocaine into general therapeutic use, numerous cases of the formation of a habit similar to that of opium or morphine, have been recorded. Some of these have been due to the attempt to substitute cocaine for morphine in the treatment of chronic morphinism, the treatment often resulting in the development of an irresistible craving for both alkaloids. The symptoms of cocainism generally begin with digestive disorders, loss of appetite, salivation and emaciation, but the more important changes occur in the central nervous system, which apparently undergoes degeneration similar to that seen in chronic morphine poisoning. Sleeplessness, tremors and occasionally convulsions, hallucinations, insanity and delirium have been noted after long abuse, along with indefinite disturbances of sensation and motion. The treatment of these cases is the withdrawal of the drug, and this can generally be done without the production of any special symptoms, though it is sometimes followed by great depression. This treatment is much facilitated by sending the patient to a special resort, and, in fact, is almost hopeless without his isolation.

Acute - evacuate stomach if taken by mouth [illegible]
Cocaine local irrit & destruction of tissues about nerves.
Eucaine - stim then depression. May be boiled. Anaesthetic. Doesn't const. vessels or dil eye. less toxic. Tropacocaine less toxic, but anaesthesia shorter. -
Alypine irrit like cocaine.
Stovaine very irritant - Novocaine less poisonous & acts only on nerves. Acts less time.

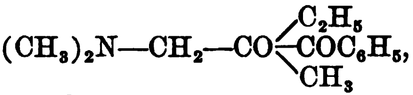
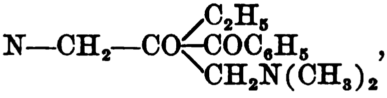
Acute Cocaine Poisoning is treated purely symptomatically. Amyl-nitrite has been advised when the blood-pressure seems much elevated, while for the convulsive attacks small quantities of chloroform or ether may be necessary. Of course, the stomach ought to be evacuated first of all if the drug has been taken by the mouth.

Give adrenalin

Substitutes for Cocaine.

A number of investigations have been made with the object of discovering some substance possessing the anæsthetic properties of cocaine without its toxicity and devoid of the local irritant and destructive action on the tissues surrounding the nerves. Several additions have already been made to the group, but none of them are entirely satisfactory, and it may be doubted whether any of them are capable of replacing it for all purposes. And in the modern use of cocaine, accidents occur from it much less often than formerly. The first of these substitutes is **Eucaine Beta-eucaine** or ($C_{15}H_{21}NO_2$), which is derived from a base analogous to ecgonine, and is less poisonous than cocaine. In animals poisoned with large doses the central nervous system is first stimulated and then paralyzed; the pulse is slowed from direct action on the cardiac muscle, and the blood-pressure falls. As a local anæsthetic it is almost as efficient as cocaine, and differs from it in not constricting the vessels or dilating the pupil. The intraocular pressure is said to be lessened, but this is not yet satisfactorily determined. A 1–2 per cent. solution of the lactate is used in the eye, 2–5 per cent. for other mucous surfaces and for subcutaneous injection. Eucaine may be employed in 1 per cent. solution instead of cocaine for infiltration anæsthesia, and is less poisonous and can be disinfected by boiling.

Tropacocaine, a compound of pseudotropine, has also been used and is less poisonous than cocaine, but also acts for a shorter time.

Stovaine,  $(CH_3)_2N{-}CH_2{-}CO{<}\begin{array}{l}C_2H_5\\ COC_6H_5\\ CH_3\end{array}$, and **Alypine,** $(CH_3)_2$- $N{-}CH_2{-}CO{<}\begin{array}{l}C_2H_5\\ COC_6H_5\\ CH_2N(CH_3)_2\end{array}$, are two nearly related bases recently introduced, which do not seem to offer any marked advantages over cocaine. Stovaine is rather less poisonous, it is true, but induces local reaction, and alypine is practically equal to cocaine in toxicity and also irritant locally.

Novocaine ($NH_2{-}C_6H_4{-}COC_2H_4N(C_2H_5)_2$), the most recently introduced of the series, is less poisonous than any of the others, and applied locally acts only on the nerves without involving the other tissues. Its anæsthetic action is less powerful and less lasting than that of cocaine, but is sufficient for most purposes when the absorption is delayed by the addition of adrenaline.

Orthoforms locally anaesthetic (Anaesthesin insol - little toxic + so is anaesthetic
insol + toxic
Dusting powder or ointment 10%. Only anaesthetic when in contact with
nerve ends. i.e. unresorbed from m.m. Maybe in gastric ulcer. Acts longer as insol.
Yohimbine - respir stimulant + cerebral excitant. No cocaine effect. Dil of sexual glands
1/12 gr = erection + increases reflexes. So in impotency.

The **Orthoforms** are local anæsthetics, which may be mentioned here, although they resemble cocaine only in their action on the sensory terminations. They are methylesters of amidooxybenzoic acid ($C_6H_3OH(NH_2)(COOCH_3)$), differing only in the positions of the hydroxyl and amido groups; *anæsthesin,* the ethylester of amidobenzoic acid, and many other similar esters have more or less local anæsthetic power. Several other aromatic derivatives have long been known to have some numbing or anæsthetic properties, but have scarcely been used in therapeutics for this purpose. Even carbolic acid has a distinct numbing effect, and some of the antipyretics have been proposed for use in ophthalmology. Orthoform is a white crystalline powder which has no taste or smell and is only very slightly soluble in water. It is used as a dusting powder or in ointment (10 per cent.), and is applied to painful surfaces, such as abrasions, ulcers or burns, either on the skin or on the visible mucous membranes (for instance, in laryngeal ulceration). In ulcer or cancer of the stomach, it has also been taken internally (0.1 G. in powder or tablets), and gives relief from the suffering. It is somewhat antiseptic and seems to be practically devoid of poisonous properties, except that slight corrosion is sometimes induced around the point of application. It has little or no effect on the sensibility of the unbroken skin, and its insolubility precludes its use by subcutaneous injection. The anæsthesia begins almost as soon as that induced by ordinary cocaine solutions, but lasts very much longer, because orthoform is dissolved and removed from the surface very slowly; thus a single application of the powder causes anæsthesia for many hours, or even for some days. On the other hand, orthoform fails to penetrate the mucous membranes as cocaine does, and therefore only anæsthetizes when it comes into actual contact with exposed nerve ends.

Yohimbine.

Yohimbine is an alkaloid ($C_{23}H_{32}N_2O_4$) obtained from the bark of the Yohimbehe tree (Corynanthe yohimbi) and resembles cocaine in some of its effects. Thus, it has the same anæsthetic action on sensory nerve terminations and on nerve trunks and in poisonous doses induces somewhat similar symptoms of stimulation of the central nervous system. It appears to increase the activity of the respiratory centre in particular, for even small quantities accelerate and deepen the respiration. The heart is hardly affected except in toxic doses, but quantities which induce no other symptoms except from the respiration dilate the vessels of the skin and of the genital organs from a direct action on the vessel walls. The last become turgid and congested from the dilation of the arterioles and erection follows. Müller states that the genital reflexes are also rendered more acute and that all the symptoms of sexual excitement are observed both in male and female animals. Yohimbine chloride and lactate have been used in veterinary medicine and also in man to induce erection and improve sexual power in cases of neurasthenic impotency and similar conditions. Dose 5 mgs. ($\frac{1}{12}$ gr.).

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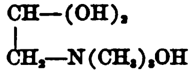
XV. PILOCARPINE AND MUSCARINE.

Pilocarpine and muscarine, two alkaloids of very different chemical constitution, possess similar properties from a pharmacological point of view. *Pilocarpine* ($C_{11}H_{16}N_2O_2$) is found along with *Isopilocarpine* in the leaves of several species of Pilocarpus.[1]

Muscarine, the alkaloid of one of the poisonous mushrooms,[2] Agaricus muscarius, or Amanita muscaria, is very closely related chemically to choline, which is a constituent of several animal tissues. It may probably be represented by the formula



$$\begin{array}{l} CH—(OH)_2 \\ | \\ CH_2—N(CH_3)_3OH \end{array}$$

A substance almost identical with muscarine from the chemical standpoint has been prepared by the oxidation of choline, but this synthetic muscarine differs in its action from the natural alkaloid in several respects. A number of other nearly related bodies (trimethylammonium bases) resemble muscarine in some points of their action, but are not so poisonous, and fail to act on several of the organs affected by the base derived from the mushroom.

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[1] The structural formula of pilocarpine is not yet definitely determined. *Pilocarpidine* has been isolated from the leaves of Pilocarpus Jaborandi only and is practically inert. *Jaborine* was formerly stated to occur with pilocarpine and to possess an action resembling that of atropine, but more recent investigators have failed to confirm either of these statements.

[2] Muscarine is accompanied in the Amanita by another poison which differs from it in inducing convulsions and other symptoms of central nervous stimulation; the symptoms of amanita poisoning are a mixture of those caused by these two poisons (Harmsen).

Muscarine (alkaloid of a poisonous mushroom) chemically unlike pilo. but their actions much the same. Stim. nerves that atropine depresses. Excessive saliva, sweat, tears, vomiting & diarrhoea. Pulse [illegible] Pupil contracted & accom. for near vision. Dyspnoea. Tremors & convulsions. All secretions stimulated, except bile, urine & milk (not under nervous control) May be lessened because of gt. loss of sweat (fluid)

Muscarine, pilocarpine and isopilocarpine resemble each other in action; muscarine is much more poisonous than pilocarpine, which is again eight times as active as isopilocarpine.

Pilocarpine and muscarine act on the same peripheral organs and apparently on the same receptive substances as atropine, but they arouse these receptors to activity while atropine depresses them. The receptors may lie on the path of impulses from the nerves to the contractile or secretory substance, and the effect of pilocarpine and muscarine is then identical with that of nerve stimulation.

Symptoms.—The symptoms of poisoning in man commence with a very marked secretion of saliva, followed soon after by excessive perspiration and a flow of tears. After muscarine and sometimes after pilocarpine, nausea, retching and vomiting, pain in the abdomen and violent movement of the intestines causing profuse watery evacuations, are next observed. The pulse is sometimes quickened, sometimes very slow and irregular; the pupil is contracted, and the sight is accommodated for near objects. The respiration is often quick and dyspnœic, and râles may be heard over the bronchi, denoting an accumulation of mucus in them. Giddiness and confusion of ideas are complained of, and after pilocarpine tremors and feeble convulsive movements are sometimes observed, but the nervous symptoms are not so conspicuous as those from the peripheral organs. Eventually the respiration becomes slower and great weakness in the movements manifests itself, but the consciousness remains more or less perfect till the breathing ceases.

Action.—The salivary and lachrymal **Glands**, the mucous glands of the mouth, throat, nose and deeper respiratory passages, the gastric secretory glands, the pancreas, and probably the intestinal glands, all secrete copiously after muscarine and pilocarpine. The sweat glands and the ceruminous glands of the ears are likewise roused to unwonted activity, and many other glandular structures are also stimulated.[1]

In most cases the solids of the secretions are increased as well as the fluids, although to a somewhat less extent. The bile, the urine and the milk do not seem to be affected directly by pilocarpine and muscarine, although they may be reduced in amount or otherwise modified by the withdrawal of large quantities of fluid from the body by other channels.

After a small quantity of atropine, pilocarpine and muscarine in ordinary quantities produce no increase in any of the secretions. This indicates that the seat of action of these poisons is not the secretory cells, for it has been shown that atropine paralyzes only the terminations of the secretory nerves and leaves the cells uninjured. On the other hand, section of the secretory nerves does not alter materially the action of pilocarpine or muscarine, for the secretion of perspiration in the foot of the cat is increased by pilocarpine even after section of the sciatic nerve. The seat of action of pilocarpine and muscarine

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[1] A curious example of this has been shown by Dreser to occur in the fish, in which the swimming bladder secretes more oxygen than usual.

at on very terminations. Glycosuria great because of stim of liver nerves
[illegible] flushing secondary to glands activity. Least but of atropine counteracts
pilocarpine muscarines gastric. Muscle. many times more powerful peripherally.
increased movements of G.I., often. bladder, pregnant uterus

is therefore the terminations of the secretory nerves—the minute fibrils which ramify between the epithelial cells and perhaps even enter them. These fibrils are stimulated by the members of this group and paralyzed by atropine, and these two series therefore form antidotes to one another.

The salivary secretion may amount to half a litre or more in the course of 2–3 hours after an injection of pilocarpine, while the skin and lungs excrete even a larger quantity of fluid in the same time. The weight is thus considerably reduced by pilocarpine owing to the loss of fluid, which may, according to some authors, amount to 2–4 kilogrammes (4½–9 lbs.) after a single dose.

The secretion of the milk is not increased by pilocarpine, but the percentage of sugar in it is stated to be larger than usual. The sugar of the blood has been found increased by pilocarpine, and this has been attributed to its acting on the terminations of the nerves in the liver which regulate the glycogenic functions of that organ.

The increased activity of the glands is accompanied by an acceleration of the blood current through them, but this is a result of their stimulation from any cause whatever, and is probably not due to the direct action of the alkaloids on the vessels. The redness of the skin, especially of the face, so often observed after pilocarpine, may perhaps be explained in this way, as an accompaniment of the augmented activity of the sweat glands.

Muscle.—Nausea and discomfort in the *stomach,* followed by retching and vomiting, are rarely seen after pilocarpine, but form some of the earliest symptoms of muscarine poisoning. They are not produced by the saliva swallowed, as was formerly supposed, but by the action of the alkaloids on the stomach, and as these symptoms are removed by atropine in small quantities, it is inferred that pilocarpine and muscarine act on the same receptors as atropine, but in the opposite sense, stimulating instead of paralyzing them. These receptors do not appear to lie in the path of nerve impulses in the stomach, as is shown by the gastric muscle still responding to stimulation of the vagus after the receptors are paralyzed by atropine.

The *intestines* are also set in unusually active movement by a similar process, and repeated evacuation of their contents follows. These are at first of firm consistency, but later, as the continued peristalsis carries down the contents of the small intestine, which have not lain long enough in the bowel to allow of the absorption of their fluid, the fæces contain more water than usual. This fluidity of the stools may also be due in part to an augmentation of the intestinal secretion, but this has not been satisfactorily demonstrated. Even after the bowel has been completely evacuated, the persistent peristalsis betrays itself in painful straining.

The muscle of a number of other organs contracts after pilocarpine or muscarine from stimulation of receptors similar to those in the stomach and bowel. Thus the *spleen, bladder* and pregnant *uterus* are contracted, and in the case of the bladder repeated evacuation and

Contraction of ciliary muscle & pupil (m) Intraocular tension reduced
Bronchial muscle spasm.

straining may occur. In some animals the uterus is inhibited by pilocarpine and muscarine, this being the usual action in the non-pregnant cat.

In some other forms of muscle, pilocarpine and muscarine cause contraction by acting on receptors which lie on the path of the nerve impulses. Thus in poisoning with these and also on local application, the *pupil* becomes extremely narrowed, and at the same time the *ciliary muscle* contracts so that the lens is accommodated for short distances. Both of these phenomena are due to stimulation of the myoneural junctions in the intraocular muscles (Fig. 29, p. 310), for atropine removes the contraction and at the same time interrupts the passage of impulses from the nerve to the muscle. This does not seem to be due to action on the anatomical ends of the nerves, for pilocarpine continues to act after these have degenerated. The point of action is therefore probably a receptor interpolated between the actual end of the nerve fibre and the contractile substance of the muscle; that the contractile substance is not affected is shown by its continuing to contract after atropine has paralyzed the pilocarpine receptor.

The intraocular pressure is reduced by muscarine and pilocarpine, although they may increase it at first. This is due to the iris being drawn up by its contraction and thus allowing free egress to the intraocular fluids (see Atropine, p. 282). The *bronchial muscles* are contracted by pilocarpine and muscarine, which here also appear to act on myoneural receptors at the terminations of the pneumogastric nerves.

All these muscular phenomena are prevented by the previous administration of atropine. This antagonistic action has been carefully studied in the eye, where it is found that after pilocarpine has produced contraction of the pupil, the administration of very small quantities of atropine is followed by dilatation. Strong pilocarpine solution again dropped into the eye will again reduce the size of the pupil, but the quantity required is vastly more than in the normal eye, and this second contraction may again be removed by comparatively small quantities of atropine. In the bird's pupil, in which the muscle is striated, muscarine and pilocarpine have no effect, the terminations of the nerves being evidently different from those in mammals.

The action of pilocarpine and muscarine on the **Circulation** presents some differences in different species of animals. On the application of either to the frog's heart, its rhythm is at once slowed, the diastolic pause being much increased in length and the contractions lessened in force. Soon the heart ceases to beat entirely, although irritation of its muscle by mechanical or chemical means elicits one or more contractions. A number of drugs which stimulate the heart muscle, such as physostigmine or digitalin, induce weak rhythmical contractions, but atropine in the minutest quantities restores the heart to its normal rhythm and strength. The symptoms produced are exactly those seen on stimulation of the vagus by electrical shocks, and muscarine has long been believed to act by stimulation of the inhibitory mechanism in the heart. Muscarine acts on the apex of the frog's ventricle, in which no ganglia whatever have been found, and must, therefore, stimulate the terminations of the vagus fibres.[1] Atropine removes this standstill by paralyzing the terminations, but larger quantities of muscarine or pilocarpine will again overcome the atropine action and restore the standstill or, at any rate, the slow pulse. Digitalin and its allies remove the standstill by increasing the irritability of the muscle until the inhibition can no longer hold the heart in check, but throughout the rhythm caused by these the activity of the vagus can be seen in the slowness of the beat and the prolongation of the diastole. The vagus ends are eventually paralyzed by pilocarpine and the heart resumes its normal rate. Larger quantities, however, again slow it owing to direct action on the cardiac muscle.

In rabbits and cats similar changes are seen in the circulation after muscarine. The heart is slowed or brought to a complete standstill, the blood pressure falls, and all the symptoms produced by anæmia of the brain may follow, but the animal becomes again perfectly normal on the administration of small quantities of atropine. Pilocarpine differs from muscarine here in several particulars, for it soon depresses the inhibitory fibres and the heart regains its former rhythm, but the cardiac muscle is then affected, so that the contractions rapidly become weaker and slower again, and this secondary slowing is not removed by atropine; the vasomotor centre also becomes gradually weakened by large doses, so that the blood vessels remain somewhat dilated, and the arterial tension remains low even after atropine.

In dogs the stimulation of the inhibitory fibres seems sometimes to be entirely absent after pilocarpine and muscarine, and in man this is very frequently the case. Instead of a slow pulse and lessened tension of the arteries, acceleration and increased blood-pressure are then observed. This is accompanied in man by marked palpitation and discomfort in the region of the heart and by dilatation of the skin vessels, especially of those of the face. In other cases, however, the same circulatory disturbances are produced as in the cat and rabbit (Fig. 30). No explanation of the acceleration of the heart has been offered, but Howell has found acceleration constantly produced by muscarine in the crab's heart.

In embryo hearts muscarine, in ordinary quantities, produces no change whatever during the first 150 hours of life (in the chick).

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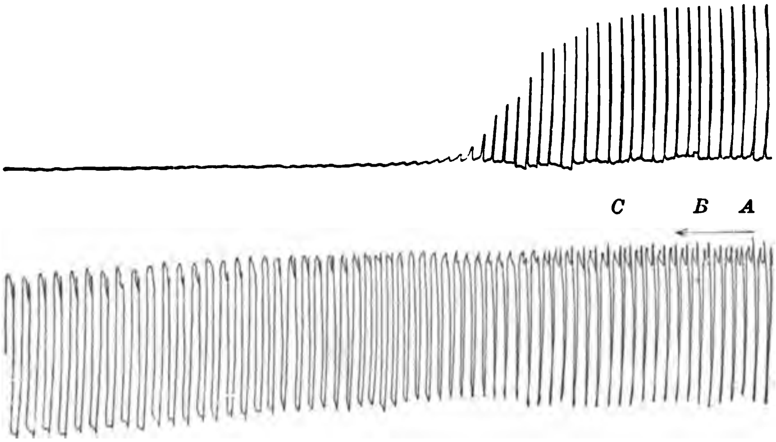
[1] This view has been contested by many authorities, who consider that muscarine and atropine act on the heart muscle directly and not through the vagus. The latest writer on the subject is Straub who has shown that muscarine acts in the course of permeating into the cells, and that when it has once reached the interior it ceases to affect the contractions. He considers that atropine antagonises muscarine by altering the permeability of the cell by the latter and is inclined to regard the effects of both alkaloids as the result of direct action on the muscle cell. It is probable that the receptors for each are not the anatomical nerve ends, but some substance in the cell which forms a link between the nerves and the contractile substance.

In man often increased rate & bp - palpitation - very variable. Often slowed.
Resp rapid etc - less blood & bronchiole constriction. Then weak & asphyxia
Spleen's action = increase of leucocytes.

The explanation of this phenomenon is that the inhibitory nerves have not been developed at this stage, and after their development is complete, muscarine acts on the heart as in the adult. The absence of slowing in some of the invertebrates may be due to a similar cause, although this does not hold good for the crab, in which there is a well-defined inhibitory apparatus.

FIG. 30.



Tracings of the movement of the auricle (upper) and ventricle (lower) of the dog under muscarine. During contraction the levers move upwards; during relaxation downwards. *A–B*, normal. At *B*, muscarine was injected intravenously and at *C* it began to act. The movements of the ventricles are slower and a distinct pause is seen in diastole. The contraction is less complete, while the heart relaxes more than usual during diastole. The auricle soon comes to a standstill in diastole. Compare the effects of stimulation of the vagus in the first part of Fig. 28, page 291.

The **Respiratory** centre is not acted on directly by small quantities of pilocarpine and muscarine. But the changes in the circulation lessen the amount of blood passing through the lungs, and the contraction of the bronchial muscle may seriously retard the movement of the air and thus impair the aëration of the blood. The œdema of the lungs which is often observed in cats and rabbits poisoned with the members of this series, and which has also occurred in fatal poisoning in man arises from the slowing of the circulation through the lungs from the cardiac action. Large quantities of pilocarpine cause a tendency to convulsive movements and a more rapid and labored respiration. Eventually the respiration becomes slow and weak and asphyxia follows.

It has been found that pilocarpine increases the **Leucocytes** of the blood from its acting on the spleen and other leucocyte-forming tissues; it is possible that the leucocytes are pressed out of the vagus by the contractions of the smooth muscle. Both polymorphonuclear and mononuclear cells are increased in the blood. Ruzicka states that the Malpighian corpuscles of the spleen are increased in number after pilocarpine.

Perspiration = reduction in fever. Tremor. hiccough & weakness. Slow resp. & fall of b.p. = all effects on lower nervous system (central). Muscarine not used - G.I. sym. & too poisonous. Pilo HCl & NO3 1/20 - 1/2 gr. Best diaphoretic. In renal dropsy. Relieves and is a stimulant to nutrition. [illegible] weak heart as depresses circ. Followed by weakness & depression occasionally nausea.

The **Temperature** is said to be increased by pilocarpine, although only to a very small extent, and the carbonic acid excretion is increased through the drug increasing the activity of the glands and other organs. After the perspiration is fully developed the internal temperature is generally reduced, especially in fever.

Some symptoms occur in cases of poisoning which point to some action of the alkaloids on the **Central Nervous System.** Thus frogs develop well-marked convulsions, and even in the higher animals and man tremor and slight convulsive movements, such as hiccough, have been observed. In the later stages muscular weakness is developed, and the slow respiration and the fall in blood-pressure also indicate a central action, which seems to be confined to the lower parts of the nervous system, however, for consciousness remains little altered. These symptoms may be complicated by marked convulsions which appear to be due to the anæmia of the brain and do not denote any direct action on that organ.

Pilocarpine and muscarine, while resembling each other in general, present some points of difference, which are of the greatest importance as regards their use in therapeutics. Muscarine has practically never been introduced into medical practice, because, while its action on the secretions is quite equal to that of pilocarpine, the gastric symptoms are produced much more readily by it. It is also a very much more powerful poison than pilocarpine, and is much less easily prepared in pure form.

PREPARATIONS.

(Muscarine is not used in therapeutics.)

✓ PILOCARPINÆ HYDROCHLORIDUM (U. S. P.) ($C_{11}H_{16}N_2O_2HCl$), the hydrochloride of an alkaloid obtained from the leaves of Pilocarpus Jaborandi or microphyllus, forms small, white crystals, odorless, with a slight bitter taste, deliquescent in the air, very soluble in water and alcohol. 0.003–0.03 G. ($\frac{1}{20}$–$\frac{1}{2}$ gr.). 1/10 - 1/2 gr

PILOCARPINÆ NITRAS (U. S. P., B. P.) ($C_{11}H_{16}N_2O_2HNO_3$), the nitrate of an alkaloid obtained from Jaborandi leaves, forms a white crystalline powder, which is soluble in 8–9 parts of cold water, and is freely soluble in hot alcohol. $\frac{1}{20}$–$\frac{1}{2}$ gr. 1/20 - 1/2

Therapeutic Uses of Pilocarpine.—Its action on the sweat glands renders pilocarpine much the most powerful diaphoretic in the pharmacopœia, and it is used internally almost exclusively for this purpose. In various conditions in which excess of fluid accumulates in the body, pilocarpine may be exhibited to remove it. In dropsy, especially that due to renal disease, a few injections frequently reduce the fluid and remove the effects of the accumulation, although they do not, of course, affect the diseased tissues directly. By unburthening the blood and tissues of their excessive fluid, however, pilocarpine may improve the nutrition of the kidney, and thereby promote its recovery. In dropsy due to heart disease pilocarpine must be used with caution, owing to its exercising a depressant action on the circulation, perhaps on the heart itself. In some other pathological exudations pilocarpine has also been advised, as in pleural, pericardial and subretinal effusion.

Hot & cold packs, theobromine, hydragogue cathartics (least weakness following)
2% to reduce intraocular tension & to contract pupil. lasts 3-5 hrs only
Abortion. Vague value in ear disease.

It must be remembered that after the diaphoresis produced by pilocarpine there usually sets in a period of depression, weakness and languor, and this may be sufficient to counteract the improvement obtained by the removal of the fluid. It is still a disputed point whether pilocarpine possesses any advantage as a diaphoretic over the other means of producing sweating, such as hot or cold packs. Its advocates point to the fact that much less disturbance of the patient is required, and that the subsequent depression is not greater, while its opponents assert that the hot or cold pack produces less depression and is not accompanied by the unpleasant salivation and occasional nausea of pilocarpine. Accumulations of fluid in the body may also be removed by way of the bowel by the use of a hydragogue cathartic or preferably a saline purgative, or the kidney may be stimulated to special activity by the use of such diuretics as theobromine and caffeine. The last method of treatment is that generally preferred as it induces less weakness and depression subsequently than either of the others.

In uræmia pilocarpine sometimes proves of great benefit if exhibited early, and it has been supposed that this was due to the skin taking up the renal function vicariously and eliminating the poison. Some support has been given this explanation by the discovery of traces of urea in the perspiration after pilocarpine, but it is now recognized that the urea is not the poisonous principle in uræmia, and the beneficial effects are probably due rather to the removal of fluid and the relief of the overstrained circulation. It has also been suggested that pilocarpine acts directly on the kidney, and an increase in the urine is not infrequently seen after several injections; but this is to be ascribed rather to the changes in the circulation following the removal of the fluid than to any direct action on the renal epithelium, for which there does not exist any satisfactory experimental evidence.

Pilocarpine has been used in a number of fevers and in diphtheria and syphilis, but no sufficient evidence of improvement in those conditions has been brought forward.

In ophthalmic surgery pilocarpine has been employed as a substitute for physostigmine, to contract the pupil and reduce the intraocular pressure. For this purpose a very dilute solution of the salts (2 per cent.) may be used, or lamellæ of gelatin may be prescribed, each containing ¼ mg. (1/250 gr.), to be laid on the conjunctiva. The contraction of the pupil generally attains its maximum in about ½–1 hour, and passes off in 3–5 hours; it is generally less complete and of shorter duration than that seen after physostigmine. Pilocarpine first increases and then lowers the intraocular tension.

In various diseases of the ear, pilocarpine has been used with good effects in some cases, but it is quite unknown how it acts here. The conditions in which it is of service are various forms of labyrinthine disease, and some forms of effusion into the tympanic cavity.

Pilocarpine was at one time used to cause contractions of the uterus in labor, and several cases of abortion have been ascribed to its use.

circ. nutrition, & secretion; scalp improved. [illegible] [illegible] [illegible] pil.
To counterbalance atropine? doubtful (doesn't affect central stim.)
In Siberia Muscarine jag, then depression.

Further experience has led to the conclusion, however, that in order to elicit this ecbolic action quantities are necessary which produce undesirable secondary symptoms.

Pilocarpine is frequently prescribed in lotions for the hair, and a renewed growth of the hair has been frequently seen in alopecia treated in this way. This has been explained by its action on the glands of the skin, increasing the moisture of the scalp and improving its circulation and nutrition, but Tappeiner found that the local application of pilocarpine to the skin produces no increase in the secretion of the glands.

In cases of atropine poisoning, large doses of pilocarpine have been ordered with alleged good results. In animal experiments, however, the quantity of pilocarpine necessary to antagonize even small doses of atropine has been found to be so large that there is little reason to hope for improvement from its administration in poisoning in man, especially as the action of atropine on the central nervous system is not antagonized by pilocarpine. In poisoning from pilocarpine or muscarine small quantities of atropine are the antidote recommended alike by pharmacological experiment and by clinical experience.

Muscarine Intoxication.—In Siberia the Agaricus muscarius is used to form an intoxicating beverage. The symptoms produced are hilarity and jollity, and the victims declare themselves to be more capable of fatiguing exertions than they would be without the preparation. Eventually giddiness and somnolence are produced, and after large quantities vomiting and convulsive attacks may follow and eventually prove fatal. The exhilarating effects are probably due to the presence of a poison discovered by Harmsen and not to the muscarine. This new poison seems to play a rôle at least as important as that of muscarine in cases of amanita poisoning; it is not antagonized by atropine, and its chemical nature is unknown.

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[1] The literature of muscarine and pilocarpine is so mixed with that of atropine, nicotine and physostigmine that a complete list would involve numerous repetitions. I must, therefore, refer those interested to the bibliography given under those groups, and shall mention here only the papers which deal very largely with muscarine and pilocarpine.

Physo or Eserine — Calabar bean. On same organs as pilocarp. Other receptors? Less effect on inhibitory nerves. Poisoning — twitching, vomiting, increased secretions, heart weak — slow, resp rapid then dyspnoei, contracted pupil, salivation, sweat, musc. weakness. Resp. paralysis.

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XVI. PHYSOSTIGMINE.

Physostigmine or Eserine is the chief alkaloid of the Calabar bean, or Ordeal bean (Physostigma venenosum), which grows in Western Africa and was employed there by the natives in the trials by ordeal for witchcraft. Either physostigmine itself, or a nearly allied alkaloid, occurs also in the Kali or Cali nuts, the seeds of Mucuna urens. The constitution of physostigmine ($C_{15}H_{21}N_3O_2$) is still unknown. Two other alkaloids have been found in the extract of the Calabar bean and possibly are products of the decomposition of physostigmine, which is a very unstable body. These are *Calabarine,* which resembles strychnine in its effects, and *Isophysostigmine,* which acts in the same way as physostigmine.

Physostigmine produces a number of symptoms resembling those of muscarine and pilocarpine poisoning; it stimulates the same organs, but may affect another set of receptors, and it has much less effect on the inhibitory nerves.

Symptoms.—The symptoms of poisoning vary but little in different animals; in the dog and rabbit the first results of a large dose of physostigmine are weakness in the voluntary movements and a curious tremor and muscular twitching, beginning in the hind legs, but soon extending over the whole body. The animal falls on one side and can not raise itself again, although it makes efforts to do so when touched. The saliva and tears are increased, the bowel is often evacuated and in the dog vomiting is common. The respiration is at first rapid and deep, and later slow and dyspnœic, the heart is weak and slow, and the pupil is contracted to a small point. These symptoms become more marked as more of the poison reaches the blood, until the respiration ceases. In cats these symptoms of depression and paralysis are preceded by a stage of increased movement and evident anxiety, but the later symptoms resemble those in the dog. In man physostigmine elicits practically the same results as in the dog, vomiting and pain in the stomach region, dyspnœa, giddiness and muscular weakness, contraction of the pupil, salivation and perspiration. The heart is slow, muscular twitching may be present and complete collapse follows. In frogs the voluntary movements disappear soon after the injection of physostigmine, the respiration ceases, and last of all the reflexes are paralyzed.

Action.—Many of these symptoms evidently arise from depression of the **Central Nervous System,** and the cause of death is the failure of

Resp + muscular central paralysis before consciousness lost
Maybe first a stimulation (respir. + b.p.). Opposed by curara.
[illegible] for epilepsy

the respiration from paralysis of the medullary centre. Some doubt exists as to what parts of the nervous system first undergo depression. Thus according to Harnack and Witkowsky, the higher centres are weakened earlier than the lower ones, but in man at any rate, the consciousness remains unimpaired after grave derangement of the respiration has manifested itself and after the muscular power is considerably depressed. This would indicate that some of the higher cerebral areas preserve their functions after others have been weakened, and several authors have therefore maintained that the depression commences in the cord and medulla oblongata, and only spreads to the cerebrum after large doses.

Another unsettled question is whether the stage of depression is preceded by one of direct stimulation of the nervous centres. Some symptoms undoubtedly point to an increase in their irritability; for example the increased respiratory movements, and to some extent the changes in the blood-pressure can scarcely be explained save by stimulation, direct or indirect.

Further evidence of the stimulant action of physostigmine on the central nervous system has been offered by its effects in epileptics, in whom the number and intensity of the seizures are increased by its use. Guinea-pigs rendered epileptic by operative procedures are also said to be more frequently attacked when physostigmine is exhibited, and even in the dog epileptiform convulsions occur occasionally, while in the cat a stage of excitement is a regular precursor of the depression. These symptoms have been explained by some writers as due to stimulation of the central nervous system, but, on the other hand, may be due to the peripheral effects of the poison, such as the constriction of the air passages by contraction of the bronchial muscles. The question as to whether any general stimulation of the central nervous system occurs in physostigmine poisoning must be left open for the present.

The muscular twitching seems to be entirely independent of the central nervous system, for it is not prevented by division of the motor nerves. This symptom is not marked in frogs, but may be so developed in mammals as to simulate convulsions, and is due to stimulation of the same receptors as are affected by curara, as is shown by the fact that the twitching is arrested by this drug. The antagonism between these two alkaloids is mutual, for the paralysis induced by curara may be removed by physostigmine applied in somewhat large doses, and animals may thus recover from quantities of curara which would otherwise prove fatal.

The **Respiration** is at first somewhat accelerated and then becomes slow and weak. The preliminary acceleration was explained by Bezold and Götz as due to stimulation of the sensory terminations in the lungs, while others regard it as evidence of central stimulation. The subsequent weakness and slowness of the breathing is undoubtedly of central origin, and death follows from the failure of the respiratory centre.

The changes in the **Circulation** require further investigation. Small doses slow the pulse and increase the blood-pressure, while larger are followed by greater slowing of the heart and a fall in the blood-pressure. The slowness of the pulse is due to the poison acting on the heart directly and not to any inhibitory interference, for it occurs

Heart slowed by X + directly: rise in bp 1) central 2) peripheral 3) contraction of intestines
[Nicotine stim. then paralyzes X gang. Muscarine stimulates X gang.
but in mammals
Physostigmine stimulates muscle. Cu depresses muscle. Atropine paralyzes X endings] but physostigmine alone = slow pulsation

after large quantities of atropine. According to several observers, the irritability of the terminations of the inhibitory fibres in the heart is increased, so that stimulation of the vagus is more effective after physostigmine. The contractions of the heart do not seem to be altered in strength in mammals, though the rhythm is slower.

The increased blood-pressure has also been the subject of some discussion. It seems independent, in part at least, of the vasomotor centre, for it is not prevented by section of the spinal cord or of the splanchnic nerves, operations which prevent impulses from the centre reaching the vessels. It may be partly due to the powerful contraction of the intestines expelling the blood from the mesenteric area, or to direct action on the muscular coats of the arterioles causing contraction and thus narrowing their calibre, or perhaps to both of these, along with some increase in the activity of the vasomotor centre.

The frog's heart beats more slowly after physostigmine, but here the individual contractions are said to be strengthened and prolonged, and there is definite evidence of stimulation of the heart muscle, which is not seen in mammals. If the vagus be stimulated in the frog after physostigmine, it produces slowing but no complete standstill of the heart, because the irritability of the muscle is so much augmented that the inhibitory apparatus can no longer entirely control it. If such a poison as muscarine produces complete standstill, physostigmine removes it, not by inducing depression of the inhibitory apparatus, but by increasing the irritability of the muscle.

The following experiment, which is mainly a repetition of one devised by Harnack, may serve to show the relationship between the effects of a whole series of poisons, which generally present some difficulties to the student. A frog, with brain and spinal cord destroyed, is stretched on a board, and its heart is exposed by the removal of a triangular piece of skin and division of the sternum. The poisons are then applied in succession by injecting them into the lymph sac, and the vagus may be exposed and placed on electrodes.

The injection of *nicotine* causes slowing of the heart (Fig. 31, *N*), followed by a return to the normal rhythm, after which vagus stimulation has no effect, while stimulation of the sinus still slows the heart. (Nicotine first stimulates and then paralyzes the ganglia on the course of the inhibitory fibres.) *Muscarine* now brings the heart to a standstill (Fig. 31, *M*), through stimulation of the terminations of the inhibitory fibres in the muscle. *Physostigmine* restores the heart to feeble rhythmic contractions (Fig. 31, *P*), through stimulation of the muscular fibres, which leads to a partial loss of control by the inhibitory apparatus. Copper salts or other muscular depressants cause a return of the standstill (Fig. 31, *C*), through neutralizing the stimulant action of physostigmine, and thus allowing the stimulated inhibitory endings to regain control. Atropine finally induces an almost complete return to the normal rhythm (Fig. 31, *A*) by paralyzing the terminations of the inhibitory nerves and thus removing the effects of the muscarine.

Here there is distinct evidence of an increase in the irritability of the cardiac muscle of the frog after physostigmine, and this is difficult to reconcile with the slow pulsation generally seen when physostigmine is given alone. In the mammalian heart no such evidence of an increase in the muscular irritability has been adduced, and the vagus arrests it as easily as before the administration of the poison; according to some investigators even more easily.

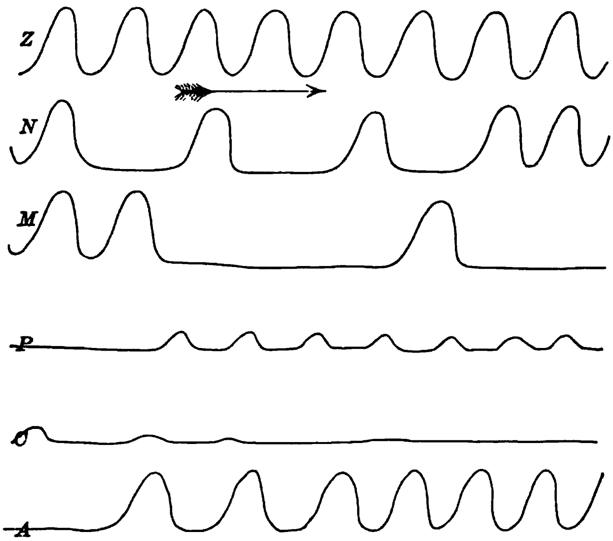
Contractions of g.i. & uterus (not acting on its inhibitory nerves) secretions (inc. pancreas) increased. Ureter, bladder, spleen, bronchial muscle in contraction. Pupil + ciliary ditto. All due to stim. of nerve endings

Physostigmine produces powerful contractions of the **Stomach, Intestine** and **Uterus** exactly resembling those elicited by muscarine and pilocarpine. It differs from these, however, in not acting on the inhibitory nerves of the uterus.

The **Secretions** are also increased by physostigmine as by pilocarpine and muscarine; thus the saliva, the tears, the perspiration, the mucous secretions and the pancreatic juice are all augmented.

FIG. 31.

Frog



normal

nicotine

muscarine

physostigmine

Cu

atropine

Tracing of the movements of the frog's ventricle. During systole the lever makes an up-stroke. *Z.* Normal. *N.* After nicotine. *M.* After muscarine. *P.* After physostigmine. *C.* After a copper salt. *A.* After atropine. (See text, p. 329.)

Besides the intestine and stomach, a number of other muscular organs are thrown into contraction by physostigmine—ureter, bladder, spleen and bronchial muscle. The **Intraocular Muscles** also undergo contraction, and their movements under physostigmine have been the subject of a large number of investigations and of a good deal of controversy. The pupil contracts when physostigmine is employed either locally or internally, and this contraction may be lessened by the subsequent application of atropine, but is not altogether removed except by large quantities. On the other hand, the dilatation of the pupil produced by small quantities of atropine may be diminished by physostigmine, but the resulting contraction is much less than that caused by physostigmine applied to the normal eye. The ciliary muscle is acted on in the same way as the pupil, so that the eye becomes accommodated for near distance, and atropine induces the same modifications. The effects of physostigmine, then, on the secretory organs, pupil and ciliary muscle are strictly analogous, and are generally attributed to the alkaloid stimulating the terminations of the nerves in these organs. Physostigmine does not contract the pupil after

III. must be intact not so for pilocarpine.
[illegible] antagonizes atropine better. Lessened intraocular tension
Mostly destroyed - some in urine.
Salicylate not deliquescent - is sol. Both S. & sulph. decompose.
1/60 gr hypo for intest atony 1/3-1% - 2-4 drops - in 1/2 hr. smallest pupil

degeneration of the motor oculi nerve (Anderson), which apparently involves its receptor; it is suggested that physostigmine acts on the terminations of the nerves in the iris, while pilocarpine and atropine, which act after degeneration, affect some receptor between these and the actual contractile substance. The antagonism of physostigmine to atropine is much more complete than that of pilocarpine, for a renewal of the contraction can be elicited much more easily by the former alkaloid. The intraocular pressure is considerably reduced by the application of physostigmine to the eye and this has generally been attributed to the contraction of the pupil facilitating the escape of the fluid by allowing it freer access to the spaces of Fontana. But the latest writer on the subject, Grönholm, states that it is due to a contraction of the intraocular vessels, which lessens the secretion.

Some physostigmine is **Excreted** in the urine, but most of that ingested is destroyed in the tissues. It has also been found in the saliva and bile.

The symptoms of poisoning with Calabar bean are identical with those caused by physostigmine, except when an old preparation containing calabarine is used, when some stimulation of the spinal cord may be induced.

PREPARATIONS.

PHYSOSTIGMINÆ SALICYLAS, eserine salicylate (U. S. P.), 0.001 G. ($\frac{1}{48}$ gr.). 1/46 gr

PHYSOSTIGMINÆ SULPHAS, eserine sulphate (U. S. P., B. P.), 0.001–0.003 G. ($\frac{1}{60}$–$\frac{1}{20}$ gr.). 1/60 - 1/20

Lamellæ Physostigminæ (B. P.), each containing $\frac{1}{1000}$ gr. of physostigmine sulphate.

The sulphate and salicylate of physostigmine are colorless or faintly yellow crystals, without odor, but possessing a bitter taste. The sulphate is deliquescent in the air and is very soluble in both alcohol and water. The salicylate is not deliquescent, has usually a slight acid reaction, and is soluble in 150 parts of cold, or 30 parts of boiling water. Both salts undergo decomposition when kept in solution and then assume a reddish-brown color; the addition of boric or sulphurous acid to the solution is said to retard this decomposition.

Therapeutic Uses.—Physostigmine has been used for its depressant action on the central nervous system in cases of abnormal excitability of the cerebral cortex. In epilepsy and chorea it has received a fairly extensive trial, but has proved of little or no service in most cases, and is positively deleterious in some. The results in the treatment with it of other diseases of the central nervous system, such as tetanus, have been no more favorable, so that it has fallen into disuse. n.b.

In recent years physostigmine has been given in pills or hypodermically (1/60 gr.) in cases of atony of the intestine leading to tympanitis and meteorism. But it is chiefly used for its action on the intraocular muscles and tension. For this purpose a solution of $\frac{1}{8}$–1 per cent. is dropped in the eye, 2–4 drops at a time, or small discs of gelatin impregnated with the alkaloid may be applied to the conjunctiva (B. P.). The pupil begins to contract in 5–15 minutes, and attains its smallest size in half an hour. It remains contracted 12–14

24 hrs - [illegible] remains contracted. Accomodation 2-4 hrs. Muscarine acts chf on accomodation; Physo. on pupil. Antagonizes atropine's dilatation. Glaucoma. Poisoning [illegible] give atropine & lavage.

hours, and according to some observers a difference in the size of the two pupils may be made out for several days. The ciliary muscle contracts along with the iris, and the eye becomes accommodated for short distances. This action on the accommodation passes off in 2–4 hours, but the sight is often rendered indistinct for some hours longer by alternate contraction and relaxation of the ciliary muscle. The action of physostigmine on the eye differs from that of muscarine, for the former acts more on the pupil, the latter on the ciliary muscle, and the pupil is often contracted by physostigmine while the accommodation is practically unchanged. The intraocular pressure is somewhat increased at first and subsequently sinks. Its action in narrowing the pupil after atropine has been made use of to remove the dilatation produced so frequently in ophthalmic surgery, but some newer tropeines, which produce a shorter mydriasis than atropine, have almost driven it from this field. It antagonizes the dilatation of the pupil after homatropine and cocaine much more successfully than that due to atropine. It has also been used in cases of synechia (attachment of the iris to the lens) alternately with atropine. The alternate contraction and dilatation of the pupil would, it was hoped, break down the attachment, but the condition is now generally treated by operation.

Physostigmine is now chiefly employed to reduce the intraocular pressure in glaucoma.

Physostigmine Poisoning has occurred only from eating the bean as yet, and is to be treated by the usual methods of evacuation of the stomach and other general measures. It has been found by Fraser that atropine acts as an antidote to physostigmine in animals, and it might be tried in cases of poisoning. The full dose of atropine is required.

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Résumé.—A number of the groups of alkaloids discussed up to this point act on the same peripheral organs and generally present some difficulty to the student, so that a few general remarks regarding them may be of service. These drugs act at two distinct points—the

See margins

Atropine has greatest affinity for nerve ends. Then physo. Then pilo then muscarine

peripheral ganglia and the terminations of the nerves in the muscular or glandular tissues. It has been shown in some instances that the points affected in these tissues do not degenerate on section of the nerve and it is possible that in all cases they are of muscular rather than of nervous origin, but this does not materially affect the argument. In the abdominal organs the receptors are often independent of the augmentor nerves. Nicotine, curara and coniine affect the ganglia (Fig. 32, *N*); muscarine, pilocarpine, physostigmine and atropine the terminations in the organs (*M*, Fig. 32). Curara, coniine and atropine are purely depressant in their peripheral action; nicotine is first stimulant and subsequently depressant, while muscarine, pilocarpine and physostigmine are practically purely stimulant. The action on the ganglia is quite independent of that on the nerve ends, and either may be stimulated or depressed after the others have been paralyzed. If, however, the nerve ends be paralyzed (Fig. 32, 2) as by atropine, changes in the ganglia will have no apparent effect, as the impulses arising from their stimulation are blocked in the nerve ends, and, on the other hand, their paralysis does not cause any further retardation of centrifugal impulses which are completely blocked already. After paralysis of the ganglia (Fig. 32, 3) the stimulation of the nerve ends is followed by the usual symptoms, because the impulses pass from the nerve ends to the epithelium directly without the intervention of the ganglia. Thus muscarine, pilocarpine and physostigmine act after the paralysis of the ganglia by nicotine or coniine. If the ganglia be paralyzed first, the paralysis of the nerve ends by atropine is followed by no change unless the latter have been in a state of activity. While it is universally acknowledged that atropine arrests the action of muscarine and pilocarpine by paralyzing the points at which these unfold their action, the subsequent stimulation of the paralyzed terminations by

FIG. 32.

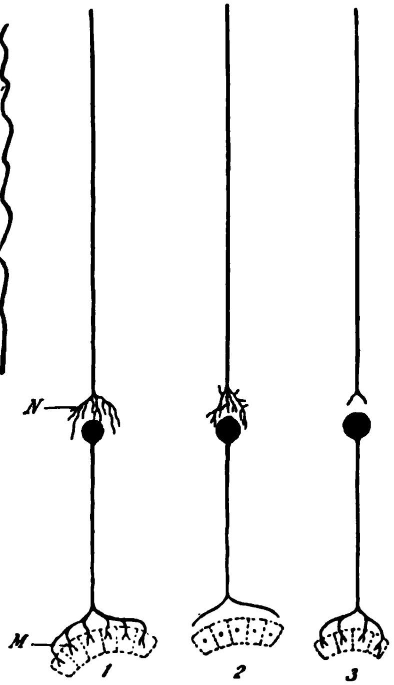


Diagram of a nerve fibre supplying a secretory gland. *N*, terminations of the cerebrospinal nerve round a ganglion cell. *M*, the terminations in the epithelium of the sympathetic fibre from the ganglion cell. In *1* the connection between the central nervous system and the secretory cells is intact, and secretions may be induced by impulses from the centres, by stimulation at *N* or at *M*. In *2* all connection between the nerve and the epithelium is broken off, and secretion can be induced only by stimulation of the secretory cells or by restoring the connection. In *3* the connection is interrupted in the ganglion, and secretion can be caused only by drugs acting directly on the epithelium or on the terminations *M*.

Adrenalin rapid rise in b.p. Heart fast, slow fast. Acts on sympath. nerves peripherally. Heart's action bettered. Splanchnics constrict, dilat. vs to skin, extremities, brain heart, lungs.

further administrations of muscarine or pilocarpine has been less readily accepted, though it is equally certain. The quantity of physostigmine required to restore them is much smaller than that of pilocarpine, and its application is therefore much more successful in reinstating the condition of active stimulation. These differences between pilocarpine and physostigmine may perhaps be explained on the analogy of the chemical theory of mass action; the "affinity" of atropine for the nerve endings is greater than that of any of the other alkaloids under discussion, that of physostigmine next, and that of pilocarpine and muscarine least. The last mentioned are therefore expelled from their combination with the protoplasm by very small quantities of atropine, and have to be given in very large quantities to remove the atropine from its combination. On the other hand, the attraction of physostigmine for the nerve ends seems much greater; larger quantities of atropine are required to displace it, and smaller quantities of physostigmine restore the activity of the nerve ends.

XVII. ADRENALINE.

The suprarenal glands of all vertebrates have been shown to contain a body which possesses a powerful action on the organism, and which the glands normally secrete into the blood-vessels. The active principle was first isolated by Abel, and has been named *epinephrine* or *adrenaline*. It is a comparatively simple substance of rather unstable character, readily passing into an inactive modification, and appears to be a feebly basic derivative of benzene, corresponding to the formula $C_6H_3(OH)_2—CHOH—CH_2—NHCH_3$. Adrenaline is lævorotary to polarized light; the dextrorotary complement has been formed synthetically and proves to have only about one-twelfth of the activity of the natural substance, while the racemic form, which consists of a mixture of these two, has rather more than one-half the activity of adrenaline (cf. Atropine and Hyoscine).

The characteristic action of adrenaline is best elicited by its injection into a vein, when it stimulates the terminations of the sympathetic nerves arising from the lumbar and dorsal regions of the spinal cord.

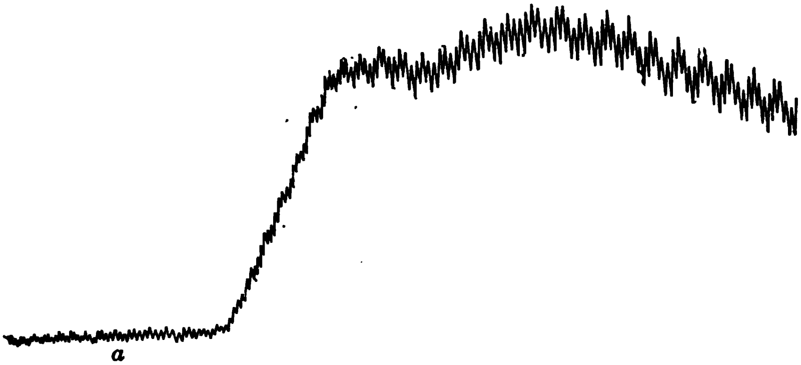
The first effects observed from the intravenous injection of adrenaline are a very marked rise in the arterial blood-pressure, accompanied at first by acceleration, then by slowing, and later again by acceleration of the heart. This rise in blood-pressure is for the most part due to constriction of the vessels of the abdominal cavity, but an increase in the efficiency of the heart similar to that seen under digitalis often plays a part, though a subordinate one. The sudden increase in pressure occurs after destruction of the vaso-motor centre and cord, or after section of the splanchnic nerves and paralysis of the ganglia on the vaso-constrictor nerves, so that it is obviously due to direct action on the muscle of the vessel walls, or on the terminations of the nerves in them. All the vessels of the body are not constricted by adrenaline, however, for those of the lungs, heart and brain are outside its sphere

Heart 1st as accelerators stim. then ē slows it secondary to high b.p. Soon v constr in vessels give way to v dil & b.p. falls & heart fast. Like digitalis but quick onset, lasts short time & secondary dil. May be maintained by subsequent injections

of action, not receiving nerve-fibres from the thoracico-lumbar cord. The blood is, therefore, diverted from the abdominal cavity to these organs, which under adrenaline become noticeably congested. And even in organs whose vessels are constricted, the degree varies considerably, apparently according to the amount of control normally exercised by the constrictor nerves; thus the vessels of the uterus are more contracted than those of the bladder, and these again more than those of the striated muscles. The terminations of the vaso-dilator fibres are also excited by adrenaline, as may be demonstrated by paralyzing the constrictor terminations by ergotoxine, when adrenaline causes a fall of blood-pressure; but in normal animals this action is entirely concealed by the stimulation of the more powerful constrictor functions.

The acceleration of the heart under adrenaline is due to stimulation of the terminations of the accelerator nerves in the heart-muscle, and is therefore accompanied by a stronger contraction and more complete evacuation of the chambers. Very soon, however, the acceleration gives place to the slow, full beat characteristic of inhibitory activity. This is very much lessened by section of the vagi and completely disappears under atropine, so that the chief cause of the slow beat is obviously excitation of the vagus centre. This excitation is not due to direct stimulation of the centre by adrenaline, but is the result of the increase in blood-pressure. After a short time, the blood-pressure beginning to fall or the vagus centre becoming exhausted, the accelerator stimulation again gains the upper hand and the pulse is much accelerated.

FIG. 33.



Tracing of the blood-pressure under the influence of extract of suprarenal gland, which was injected into the jugular vein at *a*.

The effects on the heart and vessels resemble in many points those under digitalis, but differ from these in their more rapid onset, their greater intensity and their short duration. The frog's heart is less easily affected than by digitalis, but similar changes have been observed.

The effects on the circulation, and also on other organs, last only a few minutes, but can be renewed by a fresh injection.

[illegible] on mm. not skin as not absorbed in brain etc as no sympathetic [illegible]
[illegible] relaxed. Sphincters of [illegible] tightened (as splanch. stim.). Pregnant uterus contracts.
non-pregnant relaxes. Eye - pupil dil. intraoc. tension reduced a short time - Bronch.
muscles unaffected. Myoneural action

The contraction of the vessels may be demonstrated by perfusing blood containing adrenaline through excised organs, for much less blood escapes from the vein than when blood alone is perfused. Or a solution may be applied to a mucous membrane, when the part becomes pale and anæmic from the constriction of the vessels; this is well seen when the drug is applied to the congested conjunctiva or to the mesentery. Painted on the unbroken skin adrenaline has no effect, as it fails to penetrate it, but denuded surfaces become blanched, and hæmorrhage ceases from small vessels. It has no effect when painted on the lung or on the brain, the vessels here not receiving fibres from the sympathetic.

Besides the vessels and heart, other organs innervated by the thoracico-lumbar sympathetic fibres also respond to adrenaline, the nature of the response varying with the nature of the impulses normally transmitted by these nerve-fibres. Thus, the peristaltic movements of the stomach and intestine are inhibited by splanchnic stimulation, and adrenaline has the same effect. But certain specialized parts of the bowel wall receive motor fibres from the sympathetic—the pyloric, ileo-colic and internal anal sphincters—and these are thrown into contraction by adrenaline. The movements of the gall-bladder are inhibited, and those of the gall-duct are increased by sympathetic stimulation and also by adrenaline, and many other instances of similar action have been collected by Elliott. One of the most interesting is presented by the uterus, which in the pregnant cat contracts on stimulation of the hypogastric nerves or after adrenaline, while in the non-pregnant animal both of these cause inhibition and relaxation; in the rabbit, on the other hand, both cause contraction in all cases, while in the dog both cause contraction, followed by relaxation. The reaction of the bladder to adrenaline differs in different species of animals according to the nature of the dominant impulses of the lumbar sympathetic nerves. In the eye adrenaline generally dilates the pupil, the eyelids are widely opened, the eyeball is protruded, and the nictitating membrane withdrawn, especially when the irritability of the terminations has been increased by previous section of the cervical sympathetic cord. Applied locally it constricts the vessels of the conjunctiva and dilates the pupil, and often reduces the intraocular tension for a short time. One set of unstriated muscles which fails to react in any way to adrenaline is that encircling the bronchioles, and these appear to be devoid of sympathetic innervation.

Thus adrenaline causes contraction of some forms of unstriated muscle and relaxation of others, and it therefore appears unlikely that it acts on the muscle directly. On the other hand, its effects correspond very closely with those of sympathetic stimulation, so that the inference has been drawn that it affects the terminations of the nerves. Against this it may be argued that when these nerves are cut and allowed to degenerate adrenaline still acts, but this merely indicates that the point at which adrenaline acts does not degenerate.[1]

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[1] A special term, " myoneural junction," has been coined to express this point (Elliott).

V. Con. = less urine · nervous (symp.) secretions increased – By mouth little absorbed to raise b.p. as local constriction & then destroyed. Large doses by hypo = infl. of kidney. Glycosuria etc. High b.p. = hemorrhages & atheroma Aorta

The secretions do not present such marked changes under adrenaline, though they are also generally increased when they are controlled by the sympathetic nerves. This may be due to the fact that the blood-supply is simultaneously reduced by the vaso-constriction. The saliva under adrenaline corresponds in character with that secreted on stimulation of the cervical sympathetic trunk, not with that from chorda tympani stimulation. Less urine than normal is secreted, or complete anuria may occur.

The action of adrenaline injected intravenously is of very short duration, and this was explained by its being rapidly destroyed in the tissues. Elliott states that it disappears more rapidly in those organs on which it acts than in indifferent ones, such as the lungs. But more recently it has been stated that considerable quantities remain in the blood after the effects have passed off, and some further explanation is required to explain the shortness of the action. Straub suggests that adrenaline acts only while it is entering the receptive substance and that when it has penetrated the cell it no longer influences it. When equilibrium is established between the cell and the blood therefore and no more adrenaline enters the cell, the action ceases, even though the blood still contains an excess of the principle. A new injection by increasing the concentration in the blood causes further permeation into the cell and renews the action.

Adrenaline applied locally induces such vaso-constriction that it is only slowly absorbed; and it, therefore, has only local effects when it is given by the mouth. Injected hypodermically it causes local ischæmia, but no further effects except in enormous doses. In particular the blood-pressure is seldom increased by this method of administration; injected intramuscularly it seems to have rather more general effect.

Animals are poisoned by large amounts injected hypodermically, and even smaller quantities induce glycosuria, diuresis and inflammatory changes in the liver and kidneys. Larger quantities cause prostration, collapse and paralysis of the central nervous system, ending in failure of the respiration and œdema of the lungs. Similar symptoms arise from the intravenous injection of very large quantities, but here the effects of the very high blood-pressure are also in evidence in numerous hæmorrhages. The glycosuria induced by the hypodermic injection of adrenaline in large doses has aroused a good deal of attention and speculation. It has not been shown to arise from the stimulation of sympathetic myoneural receptors as in the case of the acute symptoms, and the absence of these latter after subcutaneous administration of adrenaline suggests that the glycosuria may have a different origin. It appears to be absent in some animals after thyroidectomy. It is only induced by quantities far in excess of those used in therapeutics.

The intravenous injection of adrenaline in the rabbit often leads to atheromatous degeneration of the aorta, apparently from the strain caused by the high arterial pressure; it does not occur in other ani-

Adrenaline is the extract - 1:1000. Boil. If inject rapidly or intravenously = systemic symptoms. N.G. for Addison's. In acute circ. failure as chlor. - intravenous in saline. In inaccessible hemorrhage may form clot but high b.p. dangerous.

mals, and is said to be prevented in the rabbit by the injection of choline.

Preparations.—Extracts were at first made from the fresh glands, but soon the dried glands were introduced—*glandulæ suprarenales siccæ* (U. S. P.), the dried glands of the sheep or ox—and a watery solution made from these may be used. The active principle has been put on the market under the name of ADRENALINE,[1] and this has almost entirely supplanted the cruder preparations. It is generally used in 1 per mille solution, but often in one-tenth or even one-fiftieth of this strength. This solution may be disinfected by boiling, and does not induce any general symptoms unless when injected intravenously and rapidly. A synthetic substance, *suprarenine,* has been prepared recently. Several other nearly related substances have effects similar to adrenaline, but none of them are so active.

Therapeutic Uses.—Disease of the suprarenal gland leads to a series of symptoms known as Addison's disease, and it has been supposed that the extract of the gland might counteract this condition by supplying the substance whose deficiency induced the symptoms. As a matter of fact, however, but little success has attended its use for this purpose, and the failure may perhaps be due to the method of application, for it has been shown repeatedly that the characteristic effects of adrenaline cannot be elicited by its administration by the mouth or subcutaneously. It is possible that the extract might prove beneficial if it could be brought into the blood directly but this is quite impossible in a chronic condition such as Addison's disease. Its general action on the circulation may be taken advantage of in such emergencies as heart failure under anæsthesia or in shock, and in fact Gottlieb has shown that in animals poisoned with chloral or chloroform until the pulse has almost completely ceased, the circulation may be restored immediately by suprarenal extract. In order to elicit this action, the drug must be injected intravenously and little danger is to be apprehended from small doses if one can judge from the results in animals. In inaccessible hæmorrhage, its intravenous injection might conceivably constrict the vessels and permit of the formation of a clot, but the great rise of pressure would tend to increase the hæmorrhage, and its use is therefore hazardous.

The great use of suprarenal preparations is, however, due to its local effects on the vessels. No other body is known which induces such complete contraction of the vessels in any part to which it is applied, and in addition suprarenal extract has only local effects, unless it is injected into the blood. Complete bloodlessness of a part may thus be elicited without alteration of the general blood-pressure, and in fact without any appreciable effect upon other parts of the body. This local ischæmia has been largely employed to allow of bloodless operations on the eye and to remove congestion of the conjunctiva from various causes. It is often administered with cocaine in opera-

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[1] Other names applied to this substance are adrenine, suprarenine, suprarenaline, vasoconstrictine.

In local hemorrhage & operations – no absorption with cocaine: 1:10,000
Stomach, uterus, bladder, rectum & post partum = contraction of muscle
locally last 30 min – 2 hrs. No locally in lungs or brain
A few drops 1:1000 to Schleich's Ad = no cocaine absorption

tions on the eye (1 in 10,000 solution of adrenaline). In congestion of the nasal mucous membrane and in operations on the nose it is also used extensively and with much success; the 1 per mille solution may be sprayed into the nose, or cotton soaked in it may be packed into the cavity. In epitaxis and in operations on the nose, the hæmorrhage ceases almost completely and the contraction of the mucous membrane permits of a clearer view of the field of operation. Hay fever is often relieved by similar treatment with suprarenal preparations. A solution of adrenaline has been found useful in hæmorrhage from the ear, mouth and throat, and in controlling hæmorrhage in operations in general surgery.

Grünbaum first suggested its administration by the mouth in gastric hæmorrhage, in which the action is confined to the mucous membrane of the stomach. Similarly it may be injected into the rectum, bladder and uterus in congestion or hæmorrhage from these organs, and Schäfer recommends it especially in post-partum hæmorrhage, in which it acts not only on the uterine vessels but also on the muscular walls, and arrests the bleeding by causing a tonic contraction. In all of these cases the suprarenal preparation has to be applied directly to the bleeding organ; and no effects will follow from its being carried to them by the circulation. The local contraction of the vessels lasts very much longer than that induced by intravenous injection, for even dilute solutions induce ischæmia lasting from thirty minutes to two hours, according to the rapidity with which the adrenaline is absorbed. The vessels of some organs do not contract under adrenaline, and no benefit is to be expected from its application in hæmorrhage from these; spraying adrenaline into the lungs in case of hæmoptysis, for example, is quite useless, and similarly hæmorrhage in operations on the brain cannot be controlled by it.

The constriction of the vessels in a part to which adrenaline is applied retards the absorption of poisons injected with the adrenaline, and at the same time permits of their exercising a more marked local effect. This fact has been utilized in surgery to prevent the absorption of cocaine and intensify its local action, and the method has been attended with most encouraging results. A few drops of the 1 per mille solution are added to the Schleich's solution of cocaine, and blanching of the tissues results; instead of cocaine, any of its substitutes may be used.

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1) B.P. up less but maintained longer. ~~action~~ direct on muscle.
but renals dilate = diuresis. Second injection = no constriction
give hyp. Uterus and G.I. contract without [illegible].
5) little value in acromegaly.

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Pituitary Body.

The extracts of the **Pituitary Body,** or rather of its posterior lobe or infundibular body, have a pronounced effect when injected intravenously in animals. The chemical characters of the active principle are unknown, and it has not yet been isolated from the proteins of the gland. The arterial tension is increased by the extract, but the rise is smaller than that induced by adrenaline, although it is maintained longer. The heart is slowed, partly through inhibitory action, partly from direct action on the muscle. The rise in blood pressure is mainly the result of contraction of the arteries from direct action on them, though the vaso-constrictor centre may also be stimulated in a minor degree. A second injection made soon after this effect has been induced generally fails to raise the pressure or slow the heart; in fact the blood pressure generally falls considerably from it, owing to the presence of a second depressor body in the extract. The constrictor effect is not observed in the renal vessels, which are dilated by each injection, and this is accompanied by a profuse secretion of urine. The uterus contracts strongly after an injection of pituitary extract, while the stomach and intestines are less affected. The action appears to be exerted directly on the plain muscle of the vessels and organs, and not on the myoneural junction as in the case of adrenaline. Large quantities can be injected without inducing further symptoms than somnolence and muscular weakness. The typical action on the circulation and kidney can also be elicited by hypodermic injection of the extract, but little action is observed from its administration by the mouth. Acromegaly is generally regarded as being connected in some way with disease of the hypophysis, but the extract does not seem to modify the disorder in most cases, although improvement has been stated to occur sometimes.

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Claviceps purpura - parasitic fungus grows on rye - Secale cereale
Hydrate of ergotinine (inactive) easily converted to active ergotoxine + v.v.
Also tyramine (like adrenalin) Isoamylamine unimportant. Both in putrid meat.
Ergot acute poisoning = collapse, hemorrhages + abortion. Small doses may = gangrene + abortion

XVIII. ERGOT.

Ergot is a parasitic fungus (Claviceps purpura) which grows on the rye (Secale cereale) and occasionally on other kinds of grain; more rarely on other plants. It is of great importance in therapeutics and also in toxicology, as the use of bread and meal containing it has frequently given rise to widespread epidemics.

The chemistry of ergot has been the subject of a large number of investigations,[1] but these have been attended with little success until the last few years. The question of the chief active principles seems to have been settled by the recent work of Barger, Dale and their co-workers, who have isolated several alkaloids from the fungus. One of these, *Ergotinine,* $C_{35}H_{39}O_5N_5$, is almost inert, but its hydrate, *Ergotoxine,* $C_{35}H_{41}O_6N_5$, has a powerful action on the tissues. Either alkaloid can be readily transformed into the other, and this may explain many of the discrepancies in the literature of the subject. *Tyramine* or *Hydroxyphenylethylamine,* $OH \cdot C_6H_4 \cdot CH_2CH_2NH_2$, and *Isoamylamine,* $(CH_3)_2CHCH_2CH_2NH_2$, are also present in ergot, and the former has an important action, while the latter is in too small amount to influence the general effect of the drug. It is of interest to note that the more powerful of these two, tyramine, resembles adrenaline both in chemical constitution and in pharmacological action. Both of these amines also occur in putrid meat. In addition to the alkaloids, ergot contains a quantity of an inert oil and some saponin bodies which aid in the suspension of the more important principles in alcohol and water.

Ergot has rarely given rise to serious **Acute Poisoning** in man, but in some cases in which it was taken to procure abortion the symptoms consisted in collapse, with a weak, rapid pulse, tingling, itching and coldness of the skin, unquenchable thirst, vomiting and diarrhœa, confusion or unconsciousness, hemorrhage from the uterus, abortion and often icterus. Ecchymoses were found in the subcutaneous tissues and in many internal organs. Occasionally, after a single small dose, gangrene has supervened in small areas such as the toe-nails.

Given in therapeutic doses ergot has generally no effect except in pregnant women, in whom it often induces contraction of the uterus and evacuation of its contents. In some cases of fatal poisoning no abortion occurred.

Chronic Poisoning was formerly not uncommon, and in fact frequently gave rise to widespread epidemics, from the use of bread containing ergot after poor harvests and especially in wet seasons. Of late years these epidemics have become rare except in Russia, but some of the "plagues" of mediæval Europe may have been due to ergot poisoning.

The symptoms of ergotism are sharply divided into two groups,

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[1] These have generally resulted in the introduction of some supposed active constituent, but none of these were chemically pure and the names have now only historical interest. The best known of these names are ecboline, ergotine, sphacelinic acid, cornutine, chrysotoxine, secalintoxine, sphacelotoxine.

Ergotism I Gangrene. Skin necroses & drops. Often not abortion.
II Convulsant. Weakness, itching, vertigo, clonic convulsions. Dementia.
In cock = a comb. with gangrene of comb, tongue etc

those of gangrene and those of nervous disorders. In some epidemics both the gangrenous and the convulsive forms are present, but, as a general rule, one is much more prevalent than the other, at one time gangrene being almost invariably present, while in another epidemic, the convulsive type is the more common. The gangrene is generally developed in the limbs, especially in the fingers and toes; sometimes the whole arm or leg becomes cold and anæsthetic, dark in color, and then dry, hard and shrunken, and falls off with little or no pain and no hæmorrhage. Symptoms of such severity are rare, however, and in milder cases only the skin necroses. Gangrene of internal organs also occurs, resulting in cataract in the lens of the eye, or ulcers in the bowel and stomach, and sometimes affecting a whole organ such as a lung or the uterus. Abortion is seldom mentioned in the accounts of chronic ergot poisoning, and pregnancy seems in many cases to have run its ordinary course.

In spasmodic ergotism the first symptoms are depression, weakness and drowsiness, often with headache and giddiness, painful cramps in the limbs, and itching and formication of the skin. In severe cases paroxysmal convulsions set in, generally clonic, and often epileptiform, but leaving as sequelæ contractures in the limbs, or less often in the trunk muscles. Some intellectual weakness often follows recovery from ergot poisoning, this not infrequently amounting to complete dementia, but the disease was immediately fatal in a large proportion of cases in earlier times.

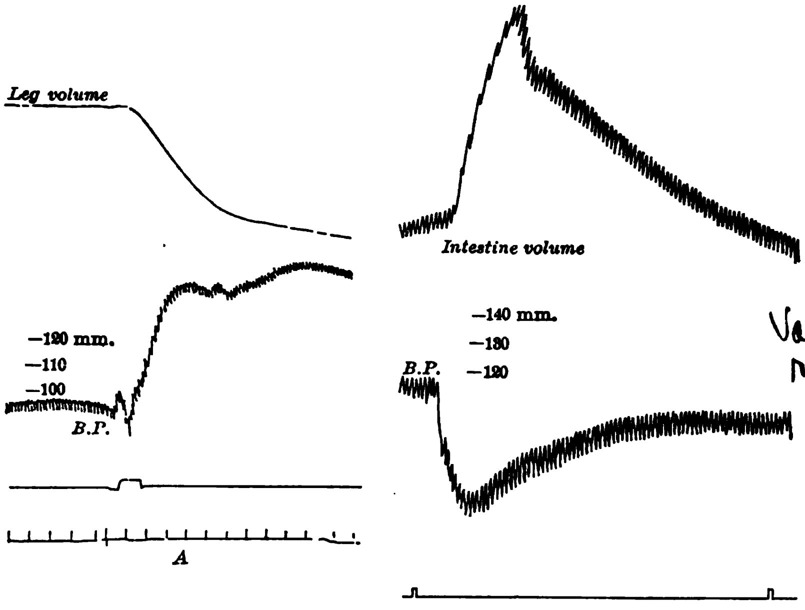
Injected into frogs ergot generally induces depression and paralysis of the central nervous system, sometimes apparently with some convulsive movements. In mammals, restlessness, salivation, sometimes vomiting and purging have been observed. Depression and weakness, ataxia and clonic convulsions follow on larger doses, which prove fatal by paralyzing the respiratory centre. Gangrene has been observed in the ears of the rabbit, but is not so common as in the pig, in which the ears, the extremities, and patches of the skin of the trunk have been found to become dry and hard, and finally to fall off. Extravasations of blood into the stomach and bowel and other organs have frequently followed the exhibition of ergot in mammals. In pregnant animals abortion is often induced, but not invariably, even when very large doses are given.

In fowls a characteristic train of symptoms is induced, and these animals have frequently been used as tests for the activity of ergot preparations. The cock becomes drowsy and dyspnœic, and the comb and wattles become dusky purple in color. Vomiting or purging may follow and a curious ataxia is observed, the animal swaying to and fro and evidently maintaining its balance with difficulty. After large or repeated doses the comb becomes dry and hard and falls off, and a similar gangrene may attack the legs, tongue or wing. The animal refuses food and becomes weak and somnolent, but may recover if the treatment be stopped.

Ergot acts on symp. myo-neural junctions (as adrenalin) Tyramine & Ergotoxine don't stim inhibitor-fibres. Latter stim motor, then large doses paralyze. Less powerful than adrenalin but last longer — may give by mouth. Ergot contains other principles which depress heart, hence B.P. less high than if its "active principles" given alone.

Action.—The action of ergot in the living organism has only recently been elucidated by the admirable experimental work of Dale, and is due to the ergotoxine and tyramine. It resembles in general character that of adrenaline, the receptors affected lying in the myoneural junctions of the sympathetic nerves from the thoracic and lumbar spinal cord. Tyramine acts less on the inhibitory terminations than adrenaline, and ergotoxine does not appear to affect them at all. And ergotoxine, while stimulating the motor myoneural junctions in small doses, paralyzes them in larger amounts. The ergot bases are much less powerful than adrenaline, but on the other hand their effects last longer and can be elicited by hypodermic injection or even by administration by the mouth.

FIG. 34.



Vaso-motor reversed

Figures illustrating the effects of ergot on the blood-pressure (Dale). In *A* the injection of ergot induces a rise of blood-pressure (B. P.) with constriction of the vessels of the leg. In *B* a large dose of ergot had been injected previously, and adrenaline injected at the point indicated now causes a fall of blood-pressure with dilatation of the intestinal vessels.

The *circulation* shows the effects which are to be expected from stimulation of the vasomotor terminations in the splanchnic area, namely, an abrupt rise of blood-pressure, when an ergot base is injected intravenously. The result is not so constant when crude ergot preparations are thus administered, as saponine bodies and other cardiac depressants mask the effect of the alkaloids. This rise in pressure occurs after section of the splanchnic nerves and is, therefore, mainly of peripheral origin. It is accompanied by constriction

Vaso-motor reversal is a drop after ergot when adrenalin [illegible]
or splanchnics stimulated [as constr. fibres depressed. & adren. then dilators
Ergot by mouth or hypo as local v. const. less marked than with adrenalin -

Tyramine directly increases rate of heart - Ergot almost as T

of the vessels of the abdominal cavity and the limbs, as may be shown by oncometer and plethysmographic records. The heart is often accelerated at first and then slowed, partly from the vagus centre being stimulated by the high blood-pressure and partly by a direct action on the heart muscle. Sometimes the slowing of the heart may be so marked as to conceal the effects of the vaso-constriction on the blood-pressure tracing.

The rise in pressure is to be ascribed to stimulation of the constrictor nerve terminations in the vessel walls and is strictly analogous to that observed under adrenaline.[1] The extent to which it is developed varies in different animals, being well marked in the cat, dog and fowl and only observed with difficulty in the rabbit and monkey.

After a large dose the same rise in pressure is observed, but if adrenaline or nicotine be injected before the pressure returns to the normal height, instead of raising the pressure, it produces a marked fall. The same is true if the splanchnic nerve be stimulated while the blood-pressure is raised by ergot, while in ordinary circumstances this raises the blood-pressure by constricting the abdominal vessels. Or, if after a large dose of ergot the pressure be allowed to return to the normal and now adrenaline be injected or the splanchnics be stimulated, no effect at all may be observed. The explanation of this remarkable change is that ergotoxine has now paralyzed the motor or constrictor terminations in the vessels, and that motor impulses, either from the splanchnic fibres or from the ganglia (nicotine) can no longer reach the muscle, nor can adrenaline act on the paralyzed terminations. But while the constrictor terminations are thus put out of activity, the inhibitory or vasodilator terminations are unaffected, and thus anything which stimulates these (*e. g.,* adrenaline) may cause a fall of pressure. The effects of adrenaline on the vasodilator terminations are ordinarily masked by its action on the more powerful constrictors.

Ergot applied locally to the arterioles has much less constricting effect than adrenaline, although some blanching may be observed. This difference accounts for the fact that the ergot action may be elicited by hypodermic injection or by administration by the mouth, while adrenaline is practically devoid of effect when given in these ways.

The heart is powerfully stimulated by tyramine, the contractions increase in rate and also in strength, and this cardiac effect must contribute to the rise of blood-pressure. It is not yet determined whether the change in the heart is due to direct action on the muscle or to stimulation of the accelerator myoneural junction. Slowing of the heart is frequently seen after an injection of ergot, and this seems to arise from stimulation of the vagus centre by the high blood-pressure and not from the direct action of the drug.

The terminations of the inhibitory nerves of the heart are not paralyzed or weakened in any way by ergot, but large doses appear to

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[1] There is reason to believe that tyramine also exercises some central action.

Less than adren. ~~[illegible]~~ GI movements lessened & sphincter stim (rather ~~[illegible]~~ inhibited to sphincters paralyzed). Intravenous of ergot = pupil const (direct action on musc
Ergot usually = uterine contractions (myoneural) as ergotoxine.
Tyramine alone may = relaxation. Ergotoxine in large ~~does~~ doses paralyze motor terminations & adrenalin fails to reinstate contractions.

weaken and depress the accelerator terminations which are derived from the thoracic sympathetic (ergotoxine).

The *stomach* and *intestine* receive motor impulses from the pneumogastric, and these are not affected by ergot. The splanchnic supplies inhibitory fibres and these are slightly stimulated by the tyramine, so that the movements cease and the tone is reduced, but these are much less affected than by adrenaline; the splanchnic motor terminations in the intestinal sphincters are paralyzed by large doses of ergotoxine.

The *pupil* undergoes a powerful constriction when ergot is injected intravenously, sometimes after a momentary dilatation. This constriction is not affected by atropine and is believed to be due to a direct action on the muscle fibre. After large doses of ergot, adrenaline fails to dilate the pupil, owing to depression of the dilator nerve fibres which originate in the thoracic region and pass upwards in the cervical sympathetic trunk. Its action on the *bladder* and *urethra* is of interest, as here the motor nerve-supply is partly derived from the lumbar and partly from the sacral nerves. It is found (Dale) that while the motor terminations from the lumbar roots are paralyzed by ergot in large doses, those from the sacral are unaffected.

The *secretory* nerves are discriminated between in the same way as the muscular. Thus it is found that in the cat large doses of ergot prevent the secretion of the submaxillary gland, which normally accompanies stimulation of the sympathetic fibres, or follows the injection of adrenaline, while stimulation of the chorda tympani, a cranial nerve, has its usual effect.

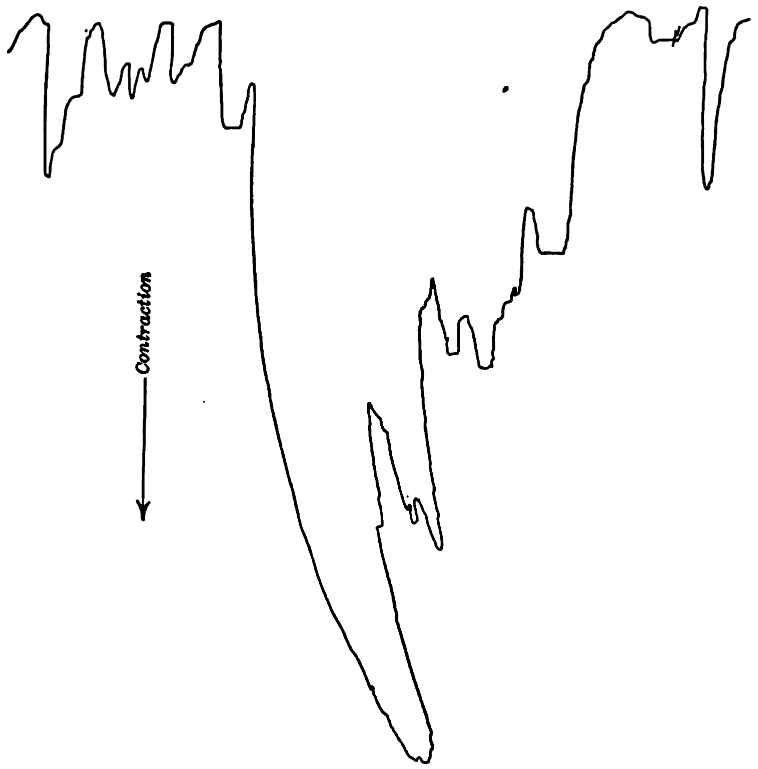
The most important effect of ergot, however, is exerted on the *uterus,* in which it stimulates primarily the motor myoneural junctions of the hypogastric nerves, while the inhibitory ones are less strongly affected. The contraction lasts for a short time and is followed by a slow relaxation, but this is interrupted by numerous new contractions, a lasting effect on the irritability being induced. Adrenaline also causes contraction of the uterus in some animals, while in others it inhibits movement and relaxes the organ; adrenaline here again stimulates both motor and inhibitory terminations, and the result, contraction or relaxation, depends on the nature of the predominating nerves. Ergotoxine, acting only on the motor endings, induces contraction only, and this is the typical effect of ergot preparations, though the tyramine injected alone may cause relaxation when the inhibitory nerves predominate, as in the non-pregnant cat. When a large amount of ergot has been injected, the motor terminations become depressed or paralyzed by the ergotoxine, and now adrenaline causes relaxation in all animals, whatever its effects before the injection of ergot.

The uterus thus reacts to ergot in a way precisely analogous to the arterioles, and it is noteworthy that from the uterus alone any very obvious symptoms are elicited by therapeutic doses. For the alimentary tract is but little affected, and the rise of blood-pressure is not

Ergot increases uterine contractions, maybe tetanic

easily observable in the circumstances in which ergot is usually exhibited. The contraction of the uterus in pregnant animals causes the descent of the fœtus toward the os, and in suitable doses ergot induces abortion. If the dose injected is small, the rhythmic contractions are accelerated and strengthened, or if the uterus is at rest, ergot may arouse it to rhythmic contraction. As the dose is increased, the contractions become more powerful and last a longer time, until with a large injection the uterus may contract very powerfully and remain in this position for many minutes.

FIG. 35.



Tracing of the uterine movements under ergot. Contraction moves the lever downward. At the point marked with the arrow ergot was injected.

The central nervous system is acted on by ergot in both man and the lower animals, but this has not as yet been elucidated by experiment and the point of action is still unknown. The depression seen especially in the fowl seems to point to cerebral action, while the marked ataxia may indicate an affection of the cerebellum. The clonic convulsions seen in mammals suggest changes in the regions of the pons and medulla. The curious permanent effects observed in spasmodic ergotism have not been explained, and no analogous symp-

CNS. action undetermined. Gangrene due to ~~shutting~~ shutting off blood supply. Vomiting probably due to non-alkaloidal constituents. 20. ext. ergotae 2 cc. Vinum ergot see

Much ergotoxine

Standardized on cock's combs.

toms have been observed from any other form of chronic alkaloidal poisoning.

The gangrenous ergotism is due to the contraction of the vessels, shutting off the blood-supply and thus leading to the death of the part.[1] It it seen more especially in the distal parts and is more liable to occur in some animals than in others. Dale states that in the fowl, which seems peculiarly liable to gangrene, the contractor action on the blood vessels is not nearly so liable to pass into the stage of paralysis of the nerve-ends as in other animals. The histological appearance of the comb in these animals is that characteristic of dry gangrene, the smaller vessels being filled with a hyaline substance with a narrow streak of red corpuscles here and there.

The vomiting and diarrhœa which are sometimes observed after ergot have not been explained. They may perhaps be due to the alkaloids, but it seems more likely that they may arise from some of the other constituents, such as choline or saponine bodies.

PREPARATIONS.

U. S. P.—**Ergota**, ergot of rye, the sclerotium of Claviceps purpurea replacing the grain of rye. When more than one year old, it is unfit for use.
Extractum Ergotæ, 0.25 G. (4 grs.). .25 G
~~FLUIDEXTRACTUM ERGOTÆ, 2 c.c. (30~~ mins.).
~~*Vinum Ergotæ*, 8 c.c. (2 fl. drs.)~~.

B. P.—**Ergota**, the sclerotium of Claviceps purpurea, originating in the ovary of Secale cereale. 20–60 grs.
Extractum Ergotæ (Ergotin), 2–8 grs.
EXTRACTUM ERGOTÆ LIQUIDUM, 10–30 mins.
Tinctura Ergotæ Ammoniata, ½–1 fl. dr.
Infusum Ergotæ, 1–2 fl. oz.— much tyramine.
INJECTIO ERGOTÆ HYPODERMICA, 3–10 mins. (subcutaneously). The injection ought to be recently prepared. It is about 33 per cent.

The fluid or liquid extracts and the hypodermic injection are the best of the preparations. The vinum is very often quite inert. The alcoholic preparations (fluidextract, extract B. P., liquid extract and tincture) contain a larger proportion of ergotoxine than the aqueous ones, the latter owing their activity to the tyramine almost exclusively. A very large number of preparations, such as ergotin, ergotinic acid, sclerotinic acid, cornutine, etc., are simply more or less purified extracts and have no advantage over the pharmacopœial preparations; in fact the chemical manipulations through which they are obtained are often such as are likely to remove, or render inert, the active bodies of the crude drug. Tyramine has recently been put on the market.

The dose of the preparations of ergot is exceedingly varied, probably because the active alkaloid, ergotoxine, tends to pass into the inactive ergotinine on keeping. At present the preparations can only be standardized by comparing their activity on the uterus or blood-pressure of animals with that of a standard preparation or with that of the alkaloids.

Therapeutic Uses.—Ergot is used very largely in obstetrics to promote the contraction of the uterus, but considerable divergence is met

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[1] Gangrene of the comb in the fowl has also been observed from the action of cantharidin, which has no effect on the vessels, and this suggests that the alkaloid of ergot may perhaps have some further action here than the vaso-constriction.

[illegible] contractions of uterus insufficient. If head not out may cause asphyxia. Be sure presentation OK. & parts soft. When head out good to prevent post-partum hemorrhage. N.G. for other hemorrhages.

Used by mouth or hypo. In subinvolution of uterus. Don't give ergot over long periods [illegible] quantity: [illegible] gangrene

with in the views of different authorities as to the special indications for its exhibition. Thus, those who believe that ergot increases the irritability of the uterus and produces rhythmical contraction without tetanus, advise that it be given whenever the pains seem insufficient, and more especially when this occurs in the later stages of labor. Others are possessed with an exaggerated apprehension of the prolonged uterine contractions, which they consider delay labor and tend to cause asphyxia in the child, and therefore advise that ergot be used only to preserve the uterus in a contracted condition after the child and placenta have been expelled. In every case the attendant should of course satisfy himself before giving ergot of the absence of all actual impediments to the passage of the child, such as contracted pelvis, abnormal presentation, or great rigidity of the soft parts, and when it is administered before the head emerges, the dose ought to be small, as otherwise the tonic contraction may be induced. When the head is about to emerge, on the other hand, a large dose may be given to promote the permanent contraction of the uterus and thus to prevent post-partum hæmorrhage. When the latter has once set in, ergot is of less immediate service, as it is slowly absorbed, and no effects follow for some twenty minues or more. Whenever there is any reason to fear that weakness of the uterine contraction and hæmorrhage may set in after the expulsion of the child, ergot ought to be given when the head emerges, and many gynecologists recommend this as a routine treatment.

Ergot hinders post-partum hæmorrhage, chiefly by promoting the contraction of the uterus. In other forms of hæmorrhage—from the stomach, intestines, kidneys, lung or uterus—in which the bleeding point cannot be reached, it is often advocated in the belief that it contracts the walls of the vessels and thus arrests the flow of blood. These hæmorrhages so often cease spontaneously that it is difficult to estimate the value of any remedy, but it may be questioned whether ergot merits its reputation in these cases. Its action in healthy animals certainly indicates that the contraction of the vessels is confined to certain organs, and there is no reason to suppose that a more intense action is exerted on a ruptured vessel than on the uninjured ones of other organs; but unless this is the case the use of ergot may be rather harmful than remedial, for any increase in the general blood-pressure, such as would follow the contraction of the vessels throughout the body, must increase the escape of blood from the injured vessel. In these cases, as in labor, the fluidextract is often given by the mouth, but this extract or the special preparation of the B. P. is sometimes injected with the hypodermic needle. It is irritant, and ought, therefore, to be injected deeply into the muscle, rather than into the subcutaneous tissues.

The effect of ergot in inducing contraction of the uterus has been used in the treatment of subinvolution and of myomata of that organ; the involution of the uterus certainly seems to be favored by it, but the results in tumor are more open to question. In any case the

— O-NO - this active (nitrates — $O-NO_2$) Nitroglycerin = ate.
+ alk = .ates + .ites.

prolonged treatment of this, or of any other condition with ergot, is to be deprecated, for if the drug is active at all, it may induce gangrene or spasmodic ergotism. The same criticism might be applied to the ergot treatment of a number of other diseases, such as aneurism, diabetes, or pneumonia; and in addition, it does not seem to have any greater effect in these than many other less dangerous remedies, which have been equally vaunted as specifics, and have been found equally valueless.

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The older literature of ergot is well given in *Grünfeld,* Arb. a. d. pharmakol. Institute zu Dorpat., vii., p. 108; xii., p. 295.

Ustilago Maydis (U. S. P.), or corn smut, a fungus growing on maize, is entirely different from ergot, and, according to Kobert, is quite inert. It has been used as a substitute for ergot, on the supposition that it would resemble it in action as well as in origin, but has proved quite ineffective.

Cotton-root Bark (Gossypii Cortex (U. S. P.)) has been used by the Southern negroes to produce abortion, and is said by some gynecologists to resemble ergot in action on the uterus. It has little or no effect on animals, except in enormous doses, and is generally stated by those who have tested it to be entirely devoid of action in man.

XIX. THE NITRITES.

The nitrites would naturally fall among the inorganic salts, but they act chiefly upon the circulation, so that it is convenient to discuss them here.

Those which have been examined more carefully are the *Nitrite of Sodium* and the *Nitrous Esters* of the methane series, especially the *Nitrite of Amyl,* which is largely used in therapeutics. In these compounds the radicle —NO is attached to the metal or alkyl through an atom of oxygen, the formulæ being $K—O—NO$, $CH_3—O—NO$, $C_3H_7—O—NO$, $C_5H_{11}—O—NO$, etc., and the chief constituent is the O—NO, the metal or radicle being of less importance. A closely allied series of bodies are the nitrates, in which the nitrogen has five affinities and is connected again to the metal or radicle by oxygen, $K—O—NO_2$, $CH_3—O—NO_2$, $C_5H_{11}—O—NO_2$, etc. The metallic nitrates differ entirely from the nitrites in their effects and will be discussed along with the other inorganic salts. Some of the *Nitric Esters,* however, undergo a reduction when brought into contact with organic matter, and nitrites are thus formed, so that these bodies have effects very similar to those of the true nitrites, and have to be discussed along with them. The best known of such nitrates is the so-called *Nitroglycerin,* which is really the trinitrate of glycerin, $(CH_2(ONO_2)CH(ONO_2)CH_2(ONO_2))$, and is broken up by alkalies into a mixture of nitrates and nitrites. The nitrates have prac-

[illegible] – [illegible]. [illegible] face, throbbing head [illegible] up.

tically no action in the small quantities given, so that almost all the effects of nitroglycerin are due to the nitrite formed. Many other organic nitrates also form nitrites in the tissues, but none of them with such rapidity as nitroglycerin.

Two which have been used to some extent in the last few years are solids —*Erythrol Tetranitrate* and *Mannitol Hexanitrate.* They act much more slowly and for a longer time than nitroglycerin.

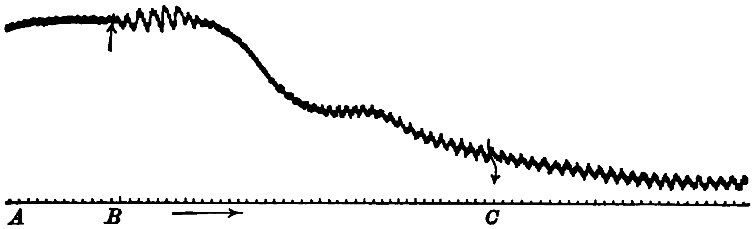
Another series of bodies which may be mentioned as occasionally acting like nitrites, although more feebly, are the nitro-bodies. In these the nitrogen is attached to the alkyl directly, and not through the intervention of an oxygen atom. Examples of these are Nitromethane, $H_3C—NO_2$, and Nitroethane, $CH_3—CH_2—NO_2$. Their action is so feeble as to preclude their use in therapeutics, and seems due to the $—NO_2$ being split off in the tissues.

The best known member of the group is **Amyl Nitrite,** and its action will first be described, while the points in which the effects of the other members diverge from it will be discussed later.

The characteristic results of the absorption of amyl nitrite are dilatation of the vessels and the formation of methæmoglobin.

Symptoms.—After the inhalation of a few drops of amyl nitrite, the face becomes flushed, and the patient complains of a feeling of fulness and throbbing in the head. Some headache and confusion is often present, the pulse is accelerated, and the respiration is somewhat quicker and deeper. The flush is often confined to the face and neck, but sometimes spreads over the whole trunk, and passes off in a few minutes, unless the inhalation is continued. If large quantities of the drug be inhaled at once, however, or if the inhalation be continued for some time, a feeling of giddiness, weakness and eventually stupor follow, the pulse becomes slow, while the respiration still remains accelerated, but is shallower and often somewhat irregular; convulsive movements may occur, but in general large quantities may be taken without actual danger in the human subject. The blood is said to have assumed a dark color in some cases, but this seems to be rare.

FIG. 36.



Tracing of the blood-pressure in the rabbit under amyl nitrite. From *A* to *B*, the blood-pressure is the normal. At *B* the inhalation was begun and the disturbance of the respiration is reflected in the blood-pressure tracing. Immediately afterwards the blood-pressure begins to fall and continues to do so even after the inhalation ceased at *C*. Note that the rhythm and strength of the pulse are comparatively little altered.

Action: Circulation.—In experiments on animals, the flushing and dilatation of the arterioles of the head is found to be accompanied

Is due to direct action on vessel muscle = dil of splanchnics & vessels of face. Depression of X center = rapid heart. Resp quick & deep - If to death = paralysis.

and followed by a profound fall in the blood-pressure. The heart is accelerated at the same time, and seems not to be responsible for the change. The cause, as has been repeatedly demonstrated, is the dilatation of the peripheral vessels, both arterioles and veins widening very considerably under the influence of the drug; the vessels of the abdominal organs and the head are more affected than those of the extremities. This widening of the vessels might be produced either by depression of the vaso-constrictor centre, or by direct action on the arterioles, but stimulation of a constrictor nerve such as the splanchnic still produces some rise in the blood-pressure, so that the nerve terminations seem to be intact, and the seat of action of amyl nitrite is therefore held to be the unstriated muscle of the arteries and veins. No satisfactory explanation has been offered for the fact that in the skin only the vessels of the head and neck should be dilated, but other facts seem to indicate that these vessels occupy an exceptional position as regards their innervation and their reactions to drugs. Darwin was the first to point out that the blush of amyl nitrite corresponds in extent with the blush produced by emotion. This blush effect seems due to the amyl in part, for other amyl esters induce it, though none to the same extent as the nitrite. The direct action on the vessel walls may be easily shown by passing blood into the artery of the amputated extremity of an animal, and measuring the amount coming from the vein. If a few drops of amyl nitrite be added to the perfused blood, the outflow from the vein is greatly increased, although here no nervous mechanism can be concerned.

The acceleration of the pulse is more marked in man and the dog than in other animals, and seems due to a depression of the inhibitory centre in the medulla oblongata, though several authors consider that a feeble, direct action on the heart is also present. The coronary arteries of the heart are dilated along with those of other parts of the body.

Large quantities of amyl nitrite slow and weaken the contractions of the heart, owing to a direct depressing action on the muscle. In the frog, the heart is usually slowed from the beginning of the application.

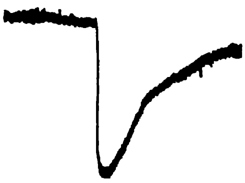
The **Respiration** is generally accelerated, and at the same time rendered deeper by amyl nitrite. Not infrequently the breath is held at first, owing to a reflex from the nasal mucous membrane, but this is not so marked as in the inhalation of more irritant vapors, such as chloroform or ether. The acceleration may be the result of the fall in pressure lessening the supply of blood to the brain. After long inhalation the respiration becomes slower and shallower and in animals death occurs from asphyxia. The walls of the pulmonary vessels are scarcely affected by the nitrites directly.

The **Kidneys** are not much affected by this series; occasionally a slight increase in the urine is observed, at other times a decrease, and after large quantities anuria may occur. The changes are evidently due to the changes in the calibre of the renal vessels. A small quan-

Of muscle = anuria. No action on nervous system

tity may widen them when they are too contracted to allow of the maximal secretion, while on the other hand, if the normal calibre is the optimal, a nitrite may lessen the secretion by lowering the general blood-pressure. When large quantities lower the pressure, they inevitably lead to a lessened secretion or anuria.

FIG. 37.



Blood-pressure under amyl nitrite taken on a very slow drum in order to demonstrate the recovery. The whole tracing occupied some six minutes. The rapid fall of pressure is followed by an almost equally rapid return to normal. (CASH & DUNSTAN.)

Small quantities of amyl nitrite seem to have no action whatsoever on the higher parts of the **Central Nervous System.** The throbbing in the head and slight confusion are evidently due to the fall in general blood-pressure. The sight is curiously affected in some people, for when a dark object on a white background is looked at, it seems surrounded by a yellow ring and that again by a blue one. In the beginning the medullary centres may be acted on reflexly from irritation of the nasal sensory terminations; the respiration is inhibited, while the blood-pressure may rise and the heart be slowed from reflex action on the inhibitory and vaso-constrictor centres respectively. Afterwards, the centres may be affected by the fall in blood-pressure giving rise to anæmia of the brain, and by the changes in the blood leading to asphyxia. The spinal cord is not acted on in mammals, but is depressed in the frog.

After large quantities convulsions are often observed; these seem to be of cerebral origin, and are probably due to the circulatory changes and the formation of methæmoglobin.

The **Peripheral Nerves** and the **Muscles** are unaffected by the inhalation of amyl nitrite, but when the frog's muscles are exposed to the direct action of the vapor, they undergo a slow passive shortening and rigor, and on periodical stimulation the contractions become rapidly weaker, until finally no response is made to the electric shock. Involuntary muscle is more easily affected than striated fibres, as has been shown by the behavior of the intestine and ureters, but even these seem less readily paralyzed than the muscle of the vessel walls, the depression and paralysis of which lead to the fall in the arterial tension, as has been already stated. The nerve terminations seem to be unaffected even by very large quantities, so that as long as a contraction of the muscles can be elicited by direct stimulation, it follows also on stimulation of the motor nerve, and the vagus terminations in the heart can transmit impulses as long as the heart continues to beat. The **Temperature** is somewhat lowered by the nitrite series, owing to the dilatation of the skin vessels, but this fall is very insignificant.

Sometimes blood chocolate colored due to methaemoglobin & nitric-oxide haemog. where O only freed after some time. Rarely leads to asphyxia. Give O. Amyl burned & sent out urine as "alk" and "nit". Best action by inhalation.

Amyl nitrite causes the **Blood** to assume a dark chocolate color, both in the body and in the test-tube. The color is due, not to any compound formed by the nitrites, but to their changing the hæmoglobin to methæmoglobin and nitric-oxide-hæmoglobin compounds in which the oxygen is attached much more firmly than in oxyhæmoglobin, and which differ from it in the absorption bands seen in the spectrum. This change in the hæmoglobin does not entail the destruction of the red corpuscles, and the compounds are eventually reduced by the tissues, although the reduction progresses much more slowly than that of ordinary oxyhæmoglobin. In man, usually very little of the hæmoglobin is thus transformed, and even after large quantities have been inhaled no abnormal coloration of the blood is noticeable, but it has been demonstrated recently that the alteration of the hæmoglobin is the cause of death in some animals, through the blood becoming incapable of carrying oxygen to the tissues. If, however, asphyxia be prevented by the inhalation of oxygen under pressure, the tissues themselves are eventually acted on. The formation of methæmoglobin does not seem to bear any relation to the action of the nitrites on the vessel walls.

Excretion.—After absorption into the blood, amyl nitrite seems to break up with the formation of nitrites of the alkalies. These undergo partial oxidation and appear in the urine in the form of nitrates and nitrites, but the quantity of these excreted is never equal to the nitrite absorbed, so that it seems probable that some part undergoes still further change and appears as one of the normal excretions. The amyl disappears, and is probably oxidized completely, although some may appear in the breath.

Nitrite of amyl given by the stomach is very much less active than when inhaled, as the nitrous acid is freed by the gastric juice and immediately decomposed. When injected subcutaneously it acts much more slowly and weakly than when absorbed by the lungs, and generally gives rise to glycosuria and slight diuresis. No satisfactory explanation of this fact has been given, but it is possible that the formation of methæmoglobin may cause partial asphyxiation of the tissues, and thus cause the formation of excess of lactic acid and glycosuria.

The pharmacopœial amyl nitrite, with which most of the experiments have been performed on which the above description is based, is not a pure substance, but consists of the nitrites of two different amyls—α-amyl and β-amyl—along with isobutyl, ethyl and propyl nitrites. A number of the pure nitrites have been examined by Cash and Dunstan, who find that in general features they resemble each other closely. The more unstable the compound, the more rapidly does the fall in blood-pressure occur, while the less easily decomposed compounds are somewhat slower in their action, but cause depression of the blood-pressure for a much longer time. The acceleration of the heart and the extent of the rigor produced in the frog's muscle

K or Na nitrite by stomach & nitrous acid — may ɔ eructation. Acts slower & longer & less some flushing or headache. Ex. in urine as Nitr

Nitroglycerine - not broken up till in blood. Acts soon & long. Not very toxic. Headache

depend also on the rapidity of the disintegration of the nitrite compound, and therefore are parallel to the fall in the blood-pressure.

The **Nitrites** of **Potassium and Sodium** act very similarly to those of the alkyls. They seem to have a more powerful action on muscular tissue, however, at any rate in the frog, for the muscles are paralyzed before the spinal cord, while after amyl nitrate the reverse is the case. They are administered by the stomach, and therefore act more slowly than amyl nitrite, but their effects last much longer. The gastric juice liberates part of the nitrous acid before absorption can occur, and it is immediately decomposed and often causes some eructation and may also give rise to irritation of the gastro-intestinal mucous membrane. The nitrite absorbed is excreted as nitrate in the urine, although some of it may remain unoxidized. The metallic nitrites do not as a rule cause so much headache and flushing of the face and neck as the alkyl compounds.

FIG. 38.

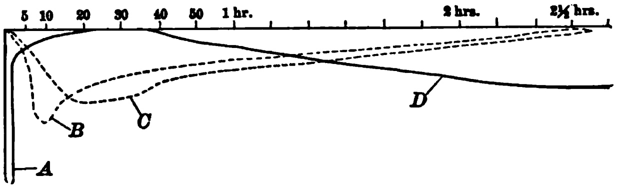


Diagram to illustrate the intensity and duration of the action of the members of the nitrite series. The extent of the fall of pressure is measured along the vertical, the duration along the horizontal line. *A*, amyl nitrite, ethyl nitrite, etc.; *B*, nitroglycerin; *C*, sodium nitrite; *D*, erythrol tetranitrate. The greatest reduction occurs in *A*, but it passes off for the most part in 5 minutes and entirely in 20. Nitroglycerin acts more rapidly than the last two, and its effects continue almost as long as those of sodium nitrite. Erythrol tetranitrate only exerts its full effect after the action of the others has passed off. (After BRADBURY.)

Nitroglycerin produces the same effects as the other members of this series, but acts much more powerfully than either the metallic or alkyl nitrites. It presents some minor points of difference, as in causing more severe headache in man. It is not decomposed in the stomach, but on reaching the blood at once breaks up into glycerin, nitrites and nitrates, in the proportion of two parts of the former salt to one of the latter. Its action commences very soon after its administration, and lasts much longer than that of amyl nitrite. The explanation of its greater activity may be that it is absorbed unchanged, but is then broken up at once, while the metallic nitrites are decomposed in the stomach and much of the nitrous acid is lost. Nitroglycerin is not wholly broken up in the human body, however, for it has been found in the urine, and the headache which so frequently follows its administration in man has been ascribed to the undecomposed molecule, and not to the nitrite constituent. It is generally supposed to be extremely poisonous, and is prescribed in exceedingly minute doses, but it has been shown that while very small quantities are sufficient to produce therapeutic effects in man, the toxic dose is enormous in animals.

Erythrol tetranitrate absorbed slowly but acts long. .05 Explosive.
Amyl for sudden attacks of angina pect. (lower bp + specific)
NaNO2 4-6 hrs prophylaxis

Several other organic nitrates have also been found to reduce the blood-pressure, and to cause the formation of methæmoglobin, but their decomposition proceeds much more slowly than that of nitroglycerin and they have not been much used in therapeutics. Erythrol tetranitrate and mannitol hexanitrate act more slowly, and the fall of pressure is more gradual, and lasts longer than under any others of the series.

PREPARATIONS.

AMYL NITRIS (B. P.), AMYLIS NITRIS (U. S. P.), a yellow, very volatile fluid, with a strong, fruity odor, soluble in alcohol and ether but rapidly decomposed by water. 2–5 drops are poured on a handkerchief and inhaled. 2-5 m A convenient preparation is the amyl nitrite "pearls," which are thin glass capsules, each containing a dose of the remedy, and one of which is broken in the handkerchief when necessary. Amyl nitrite is liable to decompose when kept long, and ought to be used only when recently prepared.

SPIRITUS GLYCERYLIS NITRATIS (U. S. P.), LIQUOR TRINITRINI (B. P.), is a 1 per cent. alcoholic solution of nitroglycerin. 0.03–0.2 c.c. (½–4 mins.). .03-.2c

TABELLÆ TRINITRINI (B. P.), or nitroglycerin tablets, are formed of chocolate and contain each $\frac{1}{100}$ gr. of nitroglycerin. 1–2 tablets. $\frac{1}{100}$ + 2

Liquor Ethyl Nitritis (B. P.), a solution in alcohol and glycerin of ethyl nitrite (2½–3 per cent.), forming a limpid liquid of apple-like odor and taste. 20–60 mins.

Sodii Nitris (U. S. P., B. P.) ($NaNO_2$), 0.05–0.1 G. (1–2 grs.). It may be prescribed in tablets or in solution. .05-.1

SPIRITUS ÆTHERIS NITROSI (U. S. P., B. P.), sweet spirits of nitre, contains only traces of ethyl nitrite, along with ether and aldehyde in alcoholic solution. When freshly prepared it acts like the other nitrites, but when prescribed along with water, as is usually the case, the nitrite escapes rapidly, and it has litle effect except from the ether and alcohol. 1–5 c.c. (20–90 mins.). 1-5c

Nonofficial.

Erythrol tetranitrate ($CH_2ONO_2(CHONO_2)_2CH_2ONO_2$) is a solid, and is recommended in doses of 0.05 G. (1 gr.), in pills, tablets or alcoholic solution. .05 G Like nitroglycerin, it is a dangerous explosive, and one fatality has already occurred in forming it into pharmaceutical preparations.

Therapeutic Uses.—The nitrites were introduced into therapeutics by Brunton, who advised their use in angina pectoris to relieve spasm of the arteries. Some question has arisen as to whether angina pectoris is generally accompanied by high arterial tension, and amyl nitrite often gives relief in cases in which the blood-pressure does not seem abnormal, so that the mechanism of its action is not completely determined. For rapid transient effects nitrite of amyl seems specially indicated, while nitroglycerin and nitrite of sodium are more suited to produce a depression of some duration. Thus during the attack of angina pectoris, amyl nitrite is often found to give instant relief, but if nitrite of soda is administered every 4–6 hours, no attack may occur. The disadvantage of the metallic nitrites is the frequent eructation they produce, while nitroglycerin often causes severe headache, which, however, disappears in some cases after repeated use.

Besides in angina pectoris the nitrite series may be used in any con-

Nitrogly. to lower resistance for heart as in Bright's + digit = better heart. NG in hemorrhage as syncope. Ditto in cardiac degener. + further lessen nutrition to heart. Used in asthma to relax. If headache due to congestion = relief. Spirit of niter a common [illegible] but [illegible] as diaphoretic & diuretic.

dition in which it is supposed that the arterial tension may be lowered with benefit to the economy. Thus nitroglycerin has been advised in heart disease and has accordingly been placed by some among the heterogeneous group of "Cardiac tonics or stimulants." Its beneficial effects are not due to any direct action on the heart, but to its decreasing the resistance against which the systole is performed. In this way the contraction of the ventricle is rendered more complete, and the output of the heart may be increased. In weak hearts struggling against a high aortic resistance, this relief may be followed by marked benefit, and for this reason nitrite preparations (nitroglycerin) are often prescribed in chronic Bright's disease. Digitalis causes a contraction of the peripheral arterioles along with its proper cardiac action, and the addition of nitrite may be advisable in some cases in order to neutralize this peripheral action. In these cases the nitrite of soda or nitroglycerin is of course preferable to amyl nitrite, whose action is too transient. Amyl nitrite has been advised in accidents during chloroform anæsthesia on the theory that it would benefit the circulation; but, as a matter of fact, it would appear strongly contraindicated in these cases, in which it is true that the heart is extremely depressed, but in which the arterial tension is practically zero. Its use is especially irrational if, as has been suggested, the failure of the respiration is partly due to anæmia of the central nervous system. The cases in which recovery has occurred after this measure may, in fact, be said to have recovered, not owing to, but in spite of the use of amyl nitrite.

Amyl nitrite has been suggested in internal hæmorrhage, on the view that by reducing the pressure in the interior of the vessels it would permit a clot to form at the point of injury. On the other hand, the dilatation of the abdominal vessels may lead to anæmia of the brain and syncope, and this has prevented the use of the drug in practice, except in unusual conditions.

In very advanced degeneration of the cardiac muscle fibre, the administration of amyl nitrite is distinctly contraindicated, for the blood-pressure is low and any further reduction may lead to syncope from anæmia of the brain, and to still greater weakness of the heart from the low pressure in the coronary arteries lessening its nutrition.

Nitrite of amyl has been used largely in asthma and in cardiac dyspnœa. Its action is often beneficial and has been attributed to its depressing the bronchial muscles, which are supposed to be in a condition of spasmodic contraction in asthma. In the cardiac cases its action in removing the dyspnœa may be due to its lowering the pressure in the systemic arteries and thus relieving the heart.

In some cases of headache, nitrite of amyl is of marked benefit, while in others it aggravates the condition. This is perfectly intelligible, as some forms of headache may be due to cerebral congestion and peripheral constriction, while others arise from anæmia of the brain.

From spasm of the circulatory organs, the use of nitrite of amyl has been extended to other forms of spasmodic seizures, such as epilepsy. It seems to be of little or no value, as indeed might be expected from its pharmacological action. In some cases it even seems to increase the tendency to convulsions.

Sweet spirits of nitre has long enjoyed a popular reputation as a diaphoretic and diuretic. It seems to have little action either on the kidneys or the sweat glands, and might be discarded from the pharmacopœia without loss. It is of more value as a carminative and flavor than for any other purpose.

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XX. THE DIGITALIS SERIES.

The digitalis series embraces a considerable number of substances which are characterized by their action on the heart. They are widely distributed in the vegetable kingdom in very different botanical families, and have long been in use for various purposes in civilized and uncivilized countries. Some of them were employed as remedies by the laity long before their virtues were recognized by the medical profession, while others have been used as arrow poisons by the natives of different parts of Africa and of the Eastern Archipelago.

The most important plants which contain bodies belonging to this group are *Digitalis purpurea* (purple foxglove), *Strophanthus hispidus,* or *Kombé,* and *Scilla maritima* (squills). Others which are less frequently used are *Helleborus niger*[1] (Christmas rose), *Convallaria majalis* (lily of the valley), *Apocynum cannabinum* (Canadian hemp), and *Adonis vernalis* (pheasant's eye). Similar effects are obtained from bodies contained in other species of these genera and in a large and ever-growing list of other plants, such as *Antiaris* (Upas tree), *Nerium* (oleander), *Acocanthera* (ouabaio), *Erythrophlœum* (sassy bark or Casca bark), *Thevetia, Urechites* and *Coronilla.*[2] Numbers of other plants are said to resemble digitalis in their effects, but until this has been shown by more careful investigation, it is undesirable to add them to the above list, which is already extensive enough. Many of the arrow poisons certainly contain digi-

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[1] This must not be confused with green and white hellebore (see page 391).

[2] Cactus grandiflorus (Cereus), which has been recommended as a substitute for digitalis, has no similar action and does not belong to this series.

Active principles mostly glucosides:- digitoxin, digitophyllin, digitalin, digitalein (digitonin dissolves them in H_2O). Digitalein alone sol in H_2O. Leaf preparations better than seed.

talin bodies, but even their botanical origin is unknown in many instances. These bodies are not, however, confined to the vegetable kingdom, for Faust has recently isolated two substances[1] from the skin of the toad, which induce the same changes in the heart. Salts of barium also induce many of the changes characteristic of this series.

The active principles of the plants of this group present many points of resemblance, and some of them which are now believed to be distinct may prove to be identical. Their isolation is attended with considerable difficulty, as many are amorphous, and but few of them form combinations with the ordinary chemical reagents. Most of them are glucosides, others are indifferent bodies, and one or two are alkaloids. There are often found in a plant several distinct bodies belonging to this series, and these may again be accompanied by others which induce the same symptoms as picrotoxin or saponin.

Digitalis has been more carefully examined from the chemical point of view than the other plants, but even its active principles are still only partially known, and the subject is yet in an unsatisfactory state; for the amount and character of the active constituents seem to vary not only in different seasons and in plants grown in different soils, but also in different parts of the same plant. The chief active principles were isolated by Schmiedeberg in 1874 and his statements have more recently been confirmed and extended by Kiliani. There appear to be at least four glucosides in digitalis which possess the characteristic cardiac action—*Digitoxin, Digitophyllin, Digitalin* and *Digitalein*—and these are accompanied by one or more glucosides (*Digitonin*) which have the irritant action of saponin and like it suspend insoluble bodies in water. The pharmacopœial preparations are made from the leaves, in which digitoxin and digitophyllin are the most important constituents, though a small quantity of another glucoside resembling digitalin is also present. These glucosides are practically insoluble in water when pure, but are taken up from the leaves by water, owing to the presence of the digitonins, so that the infusion of digitalis leaves is a very powerful preparation. The active glucosides are more soluble in alcohol, while digitonin is insoluble, so that the tincture contains practically the same constituents as the infusion except digitonin.

The seeds of digitalis are not pharmacopœial, but are extensively used for the preparation of the so-called digitalines of commerce. They contain digitalin and digitalein in large amounts with a small percentage of digitoxin and a larger proportion of digitonins than the leaves. Digitalin is less insoluble in water than digitoxin and digitalein is freely soluble. The preparations from the seeds thus differ entirely from the Galenical preparations which are formed exclusively from the leaves, and most clinicians find them less satisfactory in practice. Digitoxin is much the most powerful constituent, and the small amount in which it is present in the digitalines

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[1] These are named *Bufonin* and *Bufotalin* and appear to be nearly related to cholesterin.

Strophanthus Kombé contains the glucoside strophanthine
Scilla maritima or squills " " " scillain
Helleborus niger " " " helleborein

prepared from the seeds probably accounts for their unsatisfactory effects in therapeutics.

Strophanthus Kombé contains a crystalline glucoside, *strophanthin*, while other varieties of strophanthus, such as S. hispidus, contain another glucoside, *pseudo-strophanthin*, which is probably nearly related to strophanthin, but is about twice as poisonous. Other glucosides—*Ouabain*, *Acocantherin* and *Acocanthin*—are found in Strophanthus glaber and gratus and in Acocanthera; strophanthin is methylouabain, and acocantherin, dimethylouabain. Ouabain is the "crystalline strophanthin" of Thoms and is about twice as active as strophanthin, which again is twice as toxic as acocantherin. Some of the strophanthus genus contain non-glucosidal active bodies. The strophanthin of commerce is generally derived from a mixture of different species and varies much in composition and toxicity.

Scilla maritima, or squills, is said to contain *Scillain*, a glucoside, very soluble in alcohol, scarcely so in water, but this requires further investigation. Several other active constituents have been described in squills, but none of them have been actually isolated, and they may be merely impure forms of scillain. Saponin bodies are also present.

Helleborus niger contains *Helleborein*, a glucoside, which is very soluble in water, and resembles digitalin in action, and *Helleborin*, which is insoluble in water and has an entirely different effect.

Convallamarin (obtained from Convallaria), *Adonidin* (Adonis), *Oleandrin*, *Neriin* and *Neriodorin* (Nerium), *Euonymin* (Euonymus), *Antiarin* (Antiaris), *Thevetin* and *Cerberin* (Thevetia), *Cheiranthin* (Cheiranthus), *Coronillin* (Coronilla), *Tanghinin* (Tanghinia venenifera), are glucosides, while *Cynotoxin* or *apocynamarin* (Apocynum) is indifferent and *Erythrophlœine* (Erythrophlœum guinense) is a glucosidal alkaloid.

With the exception of the last, then, the members of this series which have been examined hitherto are either glucosides or indifferent substances, containing carbon, hydrogen and oxygen, but no nitrogen. They are all liable to decompose when kept long in watery solutions, and especially when heated with acids, and then frequently form substances which no longer possess the digitalin action, but are rather to be classed with picrotoxin. It will be shown later that even digitalin and its congeners have this picrotoxin action to a greater or lesser degree, and it seems probable, therefore, that all of them are derivatives of some common nucleus, which belongs to the picrotoxin series, but which in combination assumes a new character through its action on the heart and vessels.

Erythrophlœine and a more recently isolated alkaloid, *Muawine*, which resembles it in most respects, split off a molecule of sugar when they are boiled with acids.

Action.—The digitalis series possesses a local and a general action. The **Local Effects** consist in primary irritation, followed frequently by paralysis of the sensory nerve endings. Thus in the eye a small quantity of a solution, or a minute particle of the dry poison causes the most intense pain, redness and congestion of the conjunctiva, and all the symptoms of an acute inflammation. On the tongue the bitter taste is followed by burning pain frequently, and if the powder be

Series: – locally – intense irrit., m.m. nasal, subcut. etc. (digitalin OK)
Latter paralyzes sensory ends. hence squills emetic
Medulla stimulated: vomiting, resp. ↑, vag. & later "convulsant center"

drawn into the nostrils and larynx, marked swelling of the mucous membrane, sneezing, coughing and hoarseness are produced in many persons. They have little action on the skin, although here too smarting is occasionally produced; but when injected subcutaneously many of them cause marked inflammation, which not infrequently ends in the formation of abscesses, even although the injection has been absolutely aseptic. The same irritant action is produced in the stomach by several of them, and, in fact, by all of them when taken in very large quantities or for long periods. This irritant action is not equally marked throughout the series, however, for digitoxin is much the most powerful in this respect, while digitalin may be injected subcutaneously without danger and without pain. Their local irritant action explains the use of squills as an emetic, and of euonymus as a purgative. The local anæsthetic property is likewise not equally developed in all the members of the series; several of them (strophanthin, ouabain, erythrophlœine) have been suggested as local anæsthetics for the eye, but their primary irritant effects precludes their use for this purpose.

After absorption, the chief symptoms are due to their action on the central nervous system, the heart and the vessels, more especially on the two last. The action on the **Central Nervous System** is frequently ignored or attributed to the changes in the heart as a secondary effect, but there is undoubtedly a stimulation of some of the nerve centres, quite independent of the action on the heart and vessels. This stimulation, like that of picrotoxin, seems almost entirely limited to the medulla oblongata in many cases. In the frog the excitability of the reflexes is often lowered by members of this series, probably because of the intense stimulation of the medulla oblongata; but sometimes a distinctly increased irritability is observed. These alterations are much greater than those caused by the interruption of the circulation, and are therefore independent of the action on the heart, to which they have been erroneously ascribed. More marked symptoms are produced in mammals, however, by this central nervous stimulation, for in these vomiting is elicited very soon after the injection of large quantities, long before the heart is very seriously affected, and this is undoubtedly due to action on the medulla oblongata. To the same cause is to be attributed the rapid, deep respiratory movements and convulsions, which are often observed in the later stages of poisoning, and which are evidently not due to cerebral anæmia, as has been supposed, for the brain at this stage receives quite as much or more blood than it normally does. Even small quantities, such as are used therapeutically, cause stimulation of certain parts of the central nervous system, for the activity of the inhibitory cardiac centre in the medulla is the main cause of the slowness of the heart which is seen in therapeutics and in experiments on mammals.

The central nervous system, then, undergoes distinct stimulation under digitalis. This stimulation by small quantities seems limited to the inhibitory cardiac and the vaso-constrictor centres in the me-

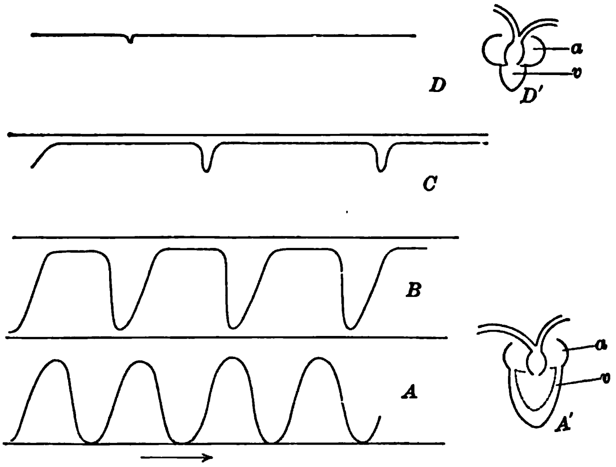
Heart - frog - slower & systole more complete & longer. Then systole does not relax & auricles are distended
corresponds to fibrillation stage in man (not capable?) prolonged systole or caused by toxins from dead heart?

dulla oblongata, but when larger doses of digitalis and its allies are injected, other parts of the medullary centres become stimulated, and vomiting, increased respiration and eventually general convulsions may be produced.

The extent to which the members of this series act as stimulants to the nervous centres varies, erythrophlœine seeming to approach more nearly to picrotoxin than the others, while helleborein is among the least active, but as yet little comparative work has been done in this direction.

The action on the **Heart** is the most important of all, and is what distinguishes digitalis and its allies from all other substances. This action has been studied most carefully in the frog, and is found to be due to an alteration in the cardiac muscular tissue. On exposing the frog's heart and watching its movements after the injection of digitalis, the muscular action can generally be made out very distinctly (Fig. 39). The heart becomes slower in rhythm, and contracts to smaller dimensions in systole, while it does not dilate so fully in diastole. The ventricle is therefore whiter during systole than normally, while during diastole it does not seem so purple, owing to its containing less blood at each period. The slowing can be seen to be due to the heart remaining contracted longer than usual, while the dilatation is very short and imperfect. Later the apex of the ventricle ceases to dilate during diastole, and remains quite still while the base still dilates after each auricular systole. Or the whole ventricle dilates only once for every two contractions of the auricle, or the two halves

FIG. 39.



Tracing of the movement of the frog's ventricle under digitalis. The lever forms an upward stroke during systole. *A*, normal; *B*, the systole is somewhat more complete and is very prolonged, and the rhythm is correspondingly slow. *C*, the ventricle remains in systole with occasional feeble diastolic movements. *D*, the diastoles of the heart have almost entirely ceased. *A′*, diagram of the heart of the frog in its normal dimensions, *a*, auricle; *v*, ventricle with the aortic bulb rising from it. The dotted line in the ventricle represents the outline in systole, the continuous line the outline in diastole. *D′*, outline of the heart in the standstill after digitalis. The ventricle *v* is very much contracted, the auricle *a* distended with blood.

X may cause heart to dilate to normal or over in diastole + the increased systole means greater output per beat. Rate may be slow (X) or fast due to direct increase in irritability. with greater or lesser diastole.

These hold for mammals, tho X usually overshadows direct stimulation

of the ventricle may contract alternately so that the blood is thrown from one side to the other. Meanwhile the duration of systole becomes still more prolonged, and the extent of diastolic dilatation diminishes until the ventricle finally ceases to relax, remaining in a position of extreme systole with its cavity obliterated. The auricles come to a standstill also, but they are unable to empty themselves into the contracted ventricle and therefore remain distended with blood. The typical action of digitalis on the muscle of the frog's heart, then, consists in a tendency to increased and prolonged contraction, and diminished and shortened diastole.

In some cases certain other features appear in the frog's heart, for the slow rhythm may be accompanied by a less perfect systole, and instead of the heart ceasing in systole, it may come to a temporary standstill in a state of extreme diastolic dilatation. This is due to stimulation of the vagus centre in the medulla, and must be carefully distinguished from the action on the cardiac muscle. Not infrequently the two forms occur in combination, or the symptoms of inhibitory action precede those of the true cardiac change.

The amount of blood expelled by the heart varies according to the degree to which each of these factors comes into play. If the dilatation in diastole is unchanged or increased, while the contraction is greater than normal, the amount of blood expelled by each beat is of course increased, but as the dilatation becomes less, the amount expelled diminishes until it reaches zero. Even though the amount of blood expelled by each beat is increased, one finds not infrequently that the total output per minute is diminished because the rhythm is so much slower than usual.

The irritability of the heart muscle is also found to be considerably increased by digitalis. Thus if the ventricle of the unpoisoned frog's heart be excised, and salt solution be led through it, it ceases to beat after some time. If, however, a small quantity of digitalis be added to the salt solution, rhythmical contractions are often induced and the heart eventually passes into systolic standstill. This increased irritability may explain a temporary acceleration of the cardiac rhythm, which is occasionally seen in frogs and in other cold-blooded animals.

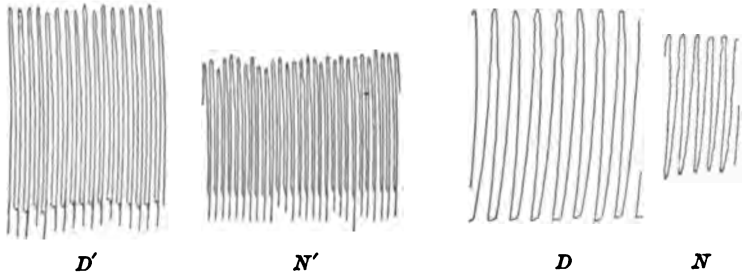
The nature of the action on the cardiac muscle has been a good deal discussed. Schmiedeberg brought forward the theory that it was mainly an increase in the elasticity of the heart muscle, but this has been disputed by Roy, who showed that it was not sufficient to explain the phenomena. With the present knowledge of the molecular changes which occur in the heart, it is impossible to proceed beyond the statement that the muscle tone is increased, and that thereby the relaxation of the muscle is rendered less perfect and the contraction more complete and prolonged. The inhibitory action of the vagus, on the contrary, tends to render the tone less complete, and to produce less complete contraction and more complete diastole. The direct effects of digitalis on the cardiac muscle of the frog are therefore diametrically opposed to those of inhibitory activity.

First or therapeutic stage :- slower but diastole prolonged + increased tone causes systole to be more complete (empties last bit) + increased contraction of papillary muscles. hence more blood out per beat

The hearts of some invertebrates, such as of the snail, are said to undergo changes similar to those described in the frog's heart, while the crustaceans seems to be entirely unaffected by digitalis.

The action on the frog's heart is of great interest, because the changes produced by this series on the mammalian heart partake largely of the same character. The inhibitory and the muscular actions are again opposed to each other, but here the inhibitory is almost invariably present to a greater or less degree. The action of digitalis and its allies on the mammalian heart may be divided into three stages, of which the first and third are always developed when sufficient quantities are administered. The second stage may be absent in certain circumstances, but is also generally present in poisoning.

FIG. 40.



Tracings of the ventricular contractions under digitalis in experiments on two dogs. *N*, *N′*, normal contractions. *D*, *D′*, contractions under digitalis. The levers move upwards during systole. In *D* the rhythm is slower and the movements extend further upwards and downwards than in *N*, *i. e.*, the contractions are more complete and the dilatation during diastole is greater. In *D′* the rhythm is slower, and the tracing extends further upwards than in *N′*, but reaches almost the same point below, *i. e.*, the contraction is stronger, but the dilatation is scarcely changed. Contrast the effects of inhibition alone in Figs. 28 and 30 (pp. 291 and 323).

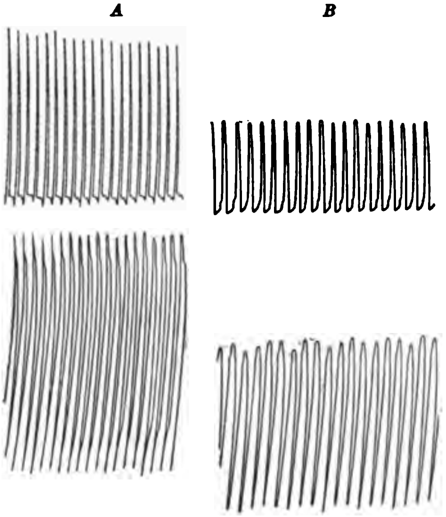
In the *first or therapeutic stage* of the action of this series, the rhythm of the heart is changed, and the extent of contraction and relaxation of the ventricle and auricle undergo certain modifications (Fig. 40). The rhythm of the heart is distinctly slower than before giving the drug, for the inhibitory apparatus is set in activity, and the slowing is accordingly due to a prolongation of the pause in diastole. The ventricles contract to a smaller size, that is, they empty themselves much more completely than they normally do. It is now universally recognized that the normal ventricle does not empty itself completely; that even at the end of its systole there still remains some blood in its interior. After the action of this group has begun, however, the blood remaining at the end of systole is much less than before. This increased contraction is, like that in the frog's heart, due to action on the cardiac muscle. The papillary muscles undergo the same changes as the rest of the ventricular wall, contracting more strongly and more completely than before the administration of the drug.

The relaxation of the ventricle is found to vary in different condi-

But if heart already dilated, digit. will cause less dil. in diastole to lessen (due to direct muscle stim. overruling I (central + periph. gang.)

tions. If the heart is weak and dilated, digitalis and its allies tend to lessen this dilatation, that is, the relaxation of the ventricle during diastole is less than before the administration of the drug. (See Fig. 41.) If, however, the heart is normal, or does not dilate much during diastole, digitalis increases the relaxation (Fig. 40, *D*). The variation in the degree of dilatation of the ventricle depends upon the opposing factors—the inhibition and the muscular action. If the inhibition be the stronger, the ventricle relaxes more completely than before, for vagus stimulation always tends to increase the relaxation of the heart. If, on the other hand, the muscular action predominates, the relaxation is lessened, for here, as in the frog's heart, this series tends to lessen the extent of relaxation. In the normal heart the application of one of this series causes, as a general rule, an increase in the extent of relaxation.

FIG. 41.



Tracings of the movements of the ventricle (lower) and auricle (upper) under digitalis. During systole the levers make an upstroke. In this experiment the inhibitory terminations had been paralyzed, so that only the muscular action is developed. *A*, normal; *B*, after digitalis. The rhythm of the heart is slightly accelerated in *B*, and the levers extend further upwards, indicating a more perfect systole in both auricle and ventricle. The ventricular lever does not reach so far downwards in *B*, *i. e.*, the ventricular diastole is less complete.

It must be added that the inhibition is due in part to stimulation of the intra-cardiac inhibitory apparatus, but mainly to the stimulation of the vagus centre in the medulla. This is shown by cutting the vagi before the injection, for the slowing is then much less than when the vagi are intact, or may be entirely absent.

If, then, the ventricles contain more blood at the beginning of systole, *i. e.*, are more relaxed than usual, and if the quantity remaining at the end of systole is less than normal, the heart must expel much more blood at each ventricular contraction that it does normally. (See Fig. 42.) Even though the amount of blood at the beginning of systole is unchanged or slightly diminished (lessened dilatation), as occasionally happens, the amount expelled is increased because the ventricles contract more completely. If the number of beats per minute remained the same, therefore, the amount of blood expelled (or the output) would be much increased; but the rhythm is slower than normal, and although each beat propels a larger amount of blood into the aorta and pulmonary artery than normally, it is not impossible that the output may be less than before the drug was administered. In the therapeutic use of these drugs the slowing is not

Due to the increased systolic contract + usual greater relaxation output is greater in spite of the slowing.
Aur: out ratio unchanged. If was irregular may become regular owing to the depression of excitability.

great enough to counterbalance the increased output per beat, and a larger amount of blood is therefore driven into the aorta and pulmonary artery.

The changes in the ventricle, then, are due to inhibitory activity and to direct cardiac action, the first tending to lessen the number of beats, to increase the relaxation of the fibres and to weaken the systole, and thus to diminish the output and efficiency of the heart; the second tending to strengthen the systole and thus to augment the output, while also limiting the dilatation, which may increase or lessen the efficiency of the heart according to circumstances.

In the auricles the same two agencies are found in opposition, the inhibitory stimulation and the muscular actions. Stimulation of the inhibitory nerves causes in the auricle more or less increase in the dilatation, while it lessens the contraction considerably, and in fact may prevent it entirely. The muscular action of this series is the same here as in the ventricle, causing a tendency towards more complete systole and less complete relaxation. After small quantities, such as are used in medicine, the rhythm of the auricle is slow, like that of the ventricle, owing to the inhibition; the relaxation is little changed, but, owing to the muscular action, the contraction is more complete. In but slightly larger quantities, however, the inhibitory action causes a less complete contraction, so that the work done by the auricle is actually less than before the injection.

FIG. 42.

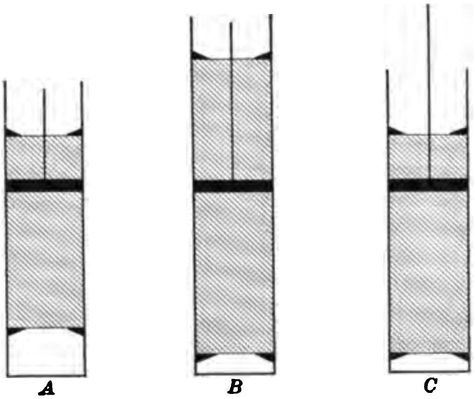


Diagram to illustrate the effect of digitalis on the output of the ventricle. *A, B, C,* three cylinders with pistons moving up and down in them and driving out fluid. In *B* and *C* (digitalis action), the piston descends lower than in *A* (normal) and in *B* it can also rise higher. The output of each stroke is represented by the shaded part of the cylinder and is greatest in *B,* in which more fluid is present at the beginning of the stroke (diastole) and less at the end of the stroke (systole) than in *A*. It is also greater in *C,* in which the same amount of fluid is present at the beginning of the stroke (diastole) as in *A,* but less is present at the end (systole). If the pistons make the same number of strokes per minute in *A, B* and *C,* the amount of fluid pumped will be greatest in *B* and least in *A,* which represents the normal ventricle.

The rhythm of the different parts of the heart is exactly the same during this stage, and the changes seen in the right auricle and ventricle correspond to those in the left.

Not infrequently a previously irregular heart becomes more regular under the influence of small doses of digitalis, and this has generally been regarded as the result of the inhibitory action, which lessens the irritability of the heart and thus reduces the tendency to premature contractions. But several investigators have recently shown that the

econd stage - n first [illegible] stage. Output per min. has become
lowering hence irregularity in systoles strength - unusual dilatation.
+50
: V. may ~~be~~ altered due to x preventing proper transmission into increased
unit of vent. Atropine eliminates this stage.

same regularizing action is exercised by digitalis in the excised heart, when there could be no question of inhibition; they therefore ascribe this result to some obscure changes induced by the muscular action of this series (Gottlieb and Magnus, Brandenburg).

If larger quantities be injected, either the inhibitory or the muscular action may become markedly increased, and the appearance of the heart varies according to which of these predominates. It must be distinctly understood that the following symptoms betoken a grave condition of poisoning and are not met with in the therapeutic use of the series.

In the *second stage* the symptoms are due to excessive inhibitory activity, while the direct cardiac action is less developed. The rhythm of the ventricle, and consequently of the pulse, is very slow and irregular, as is always the case when the inhibitory apparatus is strongly stimulated (see Fig. 28, p. 291). During diastole the ventricle dilates more completely than usual, while its systole varies in strength. If the muscular action is well developed, it continues to empty itself more completely than usual, but very often the inhibition is so powerful that the muscular action is entirely concealed and the systole is weaker and more blood remains at the end of the contraction than before the drug was administered. As a general rule, however, each beat expels more blood than normally, because the heart is engorged before the systole begins; but the rhythm is so slow that the output per minute and the efficiency of the heart as a pump is less than usual. This is the feature which differentiates the first from the second stage, in which the same factors are present; in the first stage the efficiency of the heart, *i. e.*, the amount of blood expelled per minute, is greater, in the second stage less than before the administration of the drug.

Not infrequently the auricle and ventricle beat in different rhythms, the ventricle developing a spontaneous rhythm which may be either faster or slower than that of the auricle. This is apparently due to the inhibitory action, which blocks the passage of impulses from the auricle to the ventricle, although the effect of the drug in increasing the irritability of the cardiac muscle contributes to it by facilitating the development of the spontaneous ventricular rhythm.

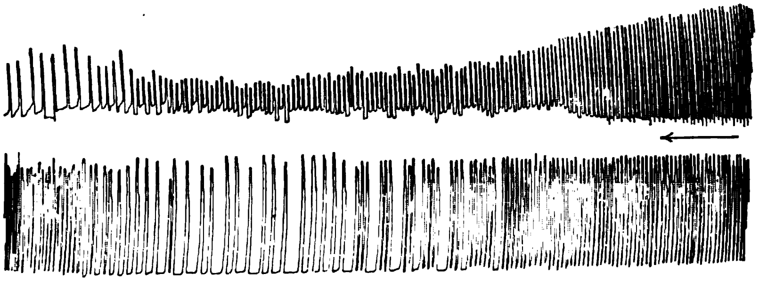
The auricular contractions are much weaker than in the first stage, and even than in the normal heart, and may cease altogether for some time, while the chambers do not tend to dilate further as a general rule.

Although the rhythms of the auricle and ventricle may differ at this stage, the two ventricles always beat in unison, and the changes in the strength of their contraction and in the extent of the relaxation are similar.

This stage of excessive inhibition is not observed in every case of poisoning in animals, nor probably in man, although in the recorded instances of poisoning with the members of this series, it seems to have been present, as the pulse is said to have been very slow and irregular.

When this very slow (40–50 per minute) and irregular pulse is met in the therapeutic use of digitalis and its allies, it indicates that the efficiency of the heart is lessened by the drug instead of being increased, and the dose should be reduced immediately. If the inhibitory mechanism is weak or is paralyzed by the preliminary injection of such drugs as atropine, the second stage is entirely absent.

FIG. 43.



Tracing of the auricular (upper) and ventricular movements (lower) under digitalis, as the first stage passes into the second. During systole the levers move upwards, during diastole downwards. The rhythm of the two chambers is at first the same, but soon changes, the auricle maintaining its rapid beat while the ventricle becomes slow and irregular. At the end of the tracing the ventricle again becomes rapid, while the auricle becomes slow. The strength of the contractions and the extent of relaxation of the ventricle muscle remain little altered, while the auricle rapidly weakens in strength, but improves again at the end of the tracing.

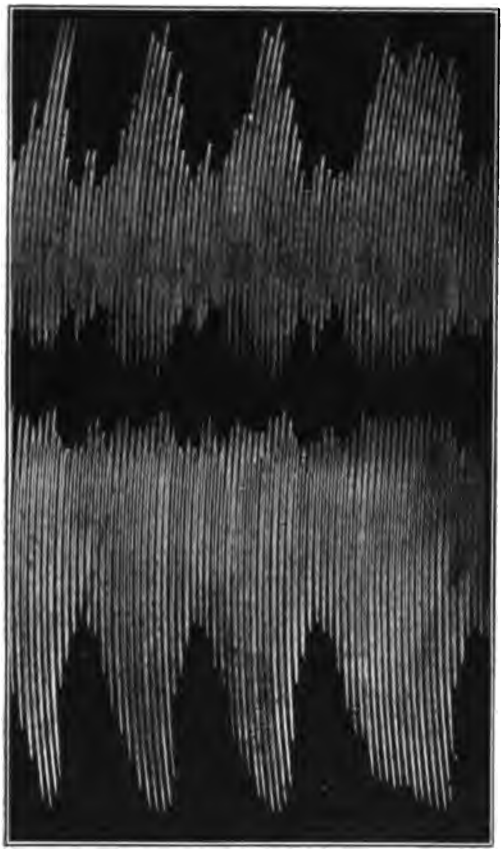
When very large quantities of any of this series are injected, the *third stage* sets in. It is preceded by the first for a short time, generally by both first and second. In this stage the ventricular rhythm becomes very much accelerated, often beyond the normal, and even beyond that seen after paralysis of the inhibitory nerves. This acceleration has often been supposed to be produced by paralysis of the vagus, but this is not the correct explanation, for stimulation of this nerve sometimes still slows the heart and always causes dilatation. The acceleration is really due to the drug increasing the irritability of the heart muscle to such an extent that the inhibitory apparatus is no longer able to hold it in check.

The auricles also undergo the same changes. They begin to accelerate their rhythm, which may continue the same as that of the ventricle for some time, but generally diverges from it in the third stage. If, however, the ventricular rhythm has been independent of the auricular in the second stage, the auricles are often later in being accelerated than the ventricles, because the inhibitory nerves act more strongly on them. The difference in rhythm of the two divisions leads to a very characteristic periodic variation in the strength of the contractions of both auricle and ventricle (Fig. 44). This auriculo-ventricular arrhythmia may continue for some time, but further irregularities soon present themselves. At intervals extrasystoles of either

Third stage: Irritability overcomes X + heart works rapidly: Irregular aur. being more controlled by X than vent. Depression of His' bundle. Often aur. or vent. beat two or three times in quick succession. Finally the increased irritability causes auricular fibrillation then vent. fibrillation + then heart dilates + op zero. Extreme irregularity in this stage.

ventricle or auricle appear, that is, two contractions follow so rapidly on each other that the chamber has no time to dilate fully between them and no blood is expelled by the second one. These extrasystoles become more numerous, and soon form groups of two or three, separated by other groups of ordinary contractions. The rhythm becomes more and more rapid, and other forms of irregularity appear, which it is impossible to describe here. Eventually the auricle generally passes into fibrillary contractions while the rhythm of the ventricle continues to increase, and the force of its contractions and the output of each beat decrease. The ventricle finally passes into fibrillary contractions also, and the circulation is arrested, after which the heart dilates to an extreme degree.

FIG. 44.



Tracings of auricle (upper) and ventricle (lower) in third stage of digitalis action. Auricle and ventricle each beating regularly but at different rates. The levers move downwards in systole, upwards in diastole.

All the features of the third stage are due to the poison's increasing the irritability of the heart muscle. This leads to acceleration of the beat, and, eventually, through the muscle of one pair of chambers being acted on more than that of the other, to arrhythmia. The extra-systoles are evidently of the same origin, and the final delirium is also to be ascribed to this action. Almost all the characteristic features of this stage may be imitated in the normal, unpoisoned heart by stimulating the different chambers by electric shocks; the impulses which in the poisoned heart arise from its own excessive irritability are here given by the artificial stimuli, but the effect is the same.

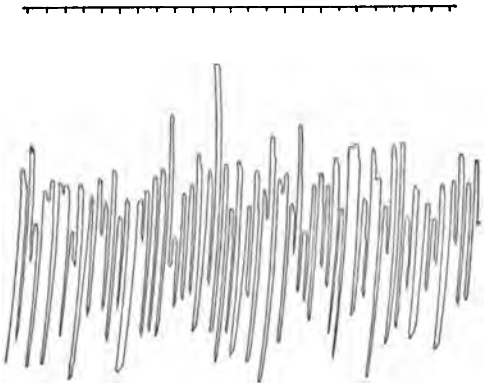
The output of the heart continues much augmented during the first part of the third stage, but, as the irregularity of the ventricles increases, and the extrasystoles become more numerous, it becomes less and eventually falls to zero when the heart passes into delirium.

Aur: which rhythm lost in II & III. Inter-vent. never.

Throughout the whole course of the intoxication the ventricles beat in unison, no interventricular arrhythmia, such as has been described by some authors, being noticeable at any stage. The two auricles also maintain the same rhythm throughout, but the rhythm of the ventricles may, as has been stated, be entirely different from that of the auricles in either the second or third stage.

The effects of digitalis on the mammalian heart therefore resemble in general those observed in the frog's. The contraction is not prolonged, however, as it is in the latter, and the inhibitory mechanism plays a more important rôle. The irregular stage evidently corresponds in each, and the final delirium cordis in the mammal represents the continued contraction in the frog, the mammalian heart not being capable of a continued systole. The heart in mammals is generally found in a condition of diastole in cases of fatal digitalis poisoning, and this has been supposed to indicate a fundamental difference in the action of digitalis on the amphibian and mammalian heart. The dilatation is not, however, a direct result of the digitalis, but is probably induced by the poisons formed in the heart by its own activity. When the mammalian heart is excised and blood containing digitalis is perfused through the coronary vessels, complete systolic standstill of the ventricle resembling that seen in the frog is often the final outcome.

FIG. 45.



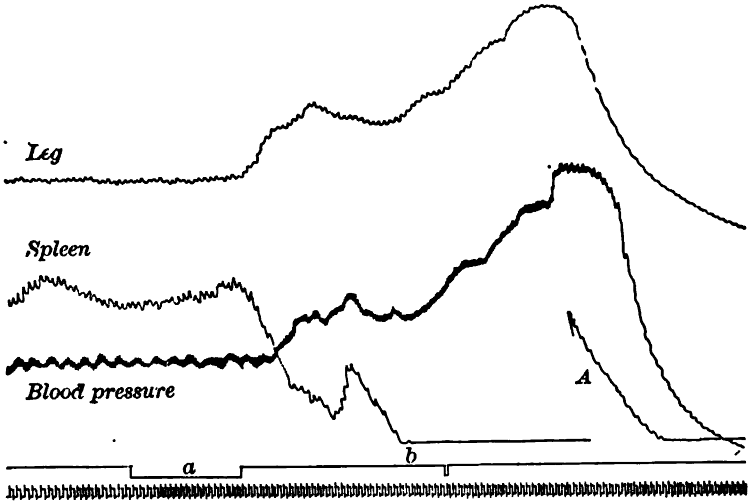
Tracing of the ventricular movements in the last stage of digitalis poisoning. The lever moves upwards in systole. The characteristic feature is the extreme irregularity, no two contractions resembling each other in form or strength.

The **Peripheral Vessels** are affected in several ways by the members of this series when large quantities are injected intravenously in animals. The increased output of the heart augments the pressure in their interior, and it seems not unlikely that the vasomotor centre is stimulated and that this causes a contraction of the arterial walls. But in addition to these effects, the muscular wall of the arterioles is constricted by a direct action of the glucosides and the resistance to the flow of blood from the arteries to the veins is increased, which further raises the tension in the aorta and larger arteries. It seems likely that all the members of the group do not act equally at all three points, but very little is known definitely on the subject except that digitoxin acts more powerfully on the vessels than some of the others, and that erythrophlœine acts more on the medulla and less on the heart than any other glucoside hitherto examined.

Vessels directly constricted (esp digitoxin). V.m. excited + heart increased. With strophanthin & digitalin extremities' vessels dilate owing to stronger splanchnic const. + to reflex v.dil.

All the digitalis bodies then increase the arterial blood-pressure partly through changes in the heart and partly through contraction of the vascular walls. There is on the one side an unusually large amount of blood expelled by the heart, on the other, unusual resistance to its passage out of the arteries. And this appears to be the final result when digitoxin is injected. But when strophanthin, digitalin or convallamarin is used, a further complication arises, for these have a somewhat less marked vascular action, and though the vessels of the abdominal organs are contracted in the same way as by digitoxin, those of the extremities dilate. This dilatation is partly owing to the increased pressure in the interior overcoming the contraction of the walls, but is mainly to be ascribed to a reflex stimulation of the vaso-dilator centre induced by the contraction of the abdominal vessels. The brain vessels react in the same way as those of the limbs, digitoxin contracting them, while under strophanthin they are little affected. The general result is that the total amount of blood circulating per unit of time is increased, but this increase is not uniform in the different organs. Thus both strophanthin and digitalis accelerate the flow through the lungs and through the peripheral muscles (Edmunds), while their effects on the abdominal organs may be to slow the current, to accelerate it, or to leave it unaltered, according to the relative degree of action on the heart and on the vessels. The rate of flow through the coronary vessels of the heart under the members of this series has been investigated by Loeb, who finds that digitoxin contracts these vessels and retards the blood supply of the heart. while strophanthin appears to have little influence on them.

FIG. 48.



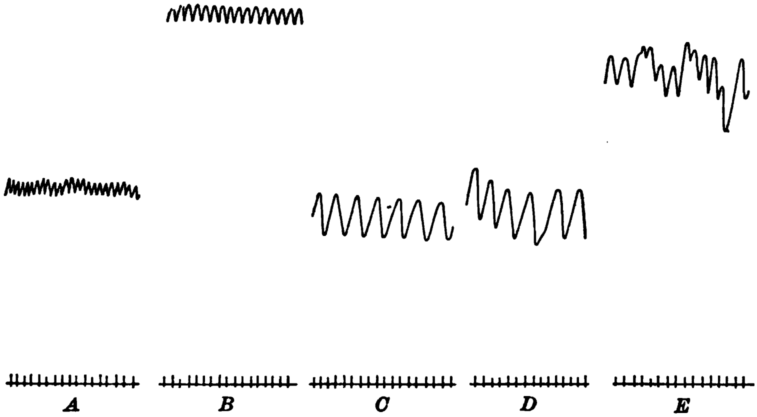
Tracings of the blood-pressure and the volume of the leg and of the spleen of the dog under strophanthus. The volume of the leg increases with the blood-pressure, *i. e.*, the vessels of the leg are dilated; that of the spleen diminishes, *i. e.*, the vessels are contracted; 10 mg. of strophanthus were injected intravenously at *a*, followed by 5 mg. at *b*. (GOTTLIEB and MAGNUS.)

So more blood on arterial side & less on venous. In man bp unchanged.
Stage I bp up, II down, III early, up, late down to 0.

It follows that under all of the series the blood tends to accumulate on the arterial side at the expense of the venous, for more blood is pumped into the arteries and it has greater difficulty in escaping. But while under digitoxin the different regions of the body appear to be equally affected, strophanthin, digitalin and convallamarin not only tend to accumulate the blood on the arterial side, but divert it from the internal organs to the limbs. It must be added that in man the therapeutic dose of digitalis and its allies does not as a general rule augment the blood-pressure perceptibly and may even reduce it slightly (p. 373).

When the extreme slowing of the *second stage* appears, the output of the heart is reduced, and the pressure in the aorta and the velocity of the blood may become subnormal (Fig. 47). When the acceleration of the *third stage* follows, the output is again augmented and may be greater than ever; the blood-pressure and velocity increase, but the heart soon becomes irregular in the force of its contractions, the output varies from second to second, and the pressure and velocity in the aorta fall slowly. The blood-pressure tracing shows the irregularity of the heart more or less accurately, but must not be taken to indicate at all the real condition of that organ, as the constriction of the arterioles varies at different times. Eventually the pressure falls to zero, when the heart ceases.

FIG. 47.



Blood-pressure tracing under digitalis. *A*, **normal;** *B*, **therapeutic stage;** *C*, **excessive inhibition causing a low blood-pressure from lessened output of the heart.** *D*, **excessive inhibition with some irregularity in rhythm.** *E*, **third stage of irregularity, during which the blood-pressure rises again from the increased output of the heart and the further contraction of the vessels.**

In the pulmonary circulation the pressure is not raised by some of the series, such as strophanthin and helleborein, while after digitalis a rise in the pressure in the pulmonary artery is sometimes seen. Yet all of them increase the output of the right ventricle. The explanation of this paradox probably is that the pulmonary vessels can contain not only the ordinary supply of blood, but also an increased

Urine increased esp in dropsy due to increased renal b.p. yet large doses contract vessels enough to prevent this (Caffeine acts directly on tubules) Solids not increased. May be some local irritant action (of squills)

volume without offering any great resistance. In the later stages the pulmonary circulation presents irregularities similar to those of the systemic.

Action on the **Renal Secretion.**—When digitalis was first introduced to the notice of the medical profession by Withering its action on the heart was not appreciated. Withering used it only to remove accumulations of fluid from the body, which it accomplished by increasing the secretion of urine. This observation of Withering was soon confirmed by further experience in the use of this drug, but it was long disputed whether this diuretic action occurred in health, or whether it was not confined to cases in which pathological accumulations of fluid were present. Digitalis, however, as is now conceded by almost everyone, causes some increase in the quantity of urine secreted by the normal animal, although this is small compared with that in cases of dropsy. The fluid of the urine is much more largely augmented than the solids, which may remain unchanged. The cause of this increase in the renal secretion is not generally believed to be a direct action on the secretory mechanism, such as it met with under caffeine; on the contrary, the kidneys themselves are supposed to be acted on only indirectly through the changes in the circulation. Small doses are said to increase the bloodstream through the kidney and thus to increase the renal volume as measured in the oncometer, while larger doses contract the renal vessels along with those of the other

FIG. 48.

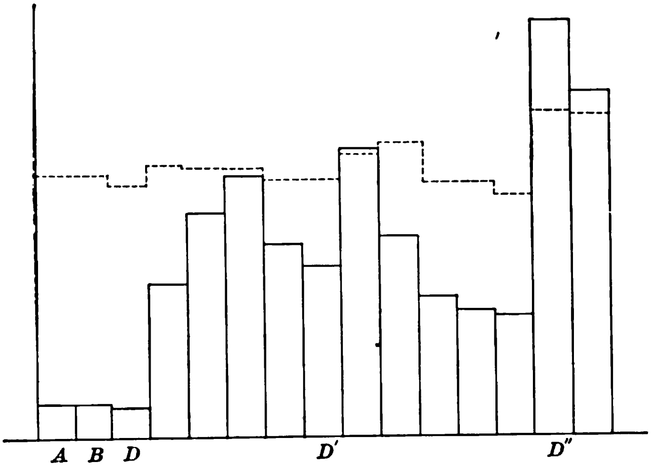


Diagram representing the secretion of urine in a rabbit under digitalis. Each rectangle represents the amount of urine secreted in ten minutes. *A* and *B*, normal secretion. In the next ten minutes a small dose of digitalis *D* was injected intravenously and a rapid increase in the secretion followed. At *D′* and *D″* further injections were made, each being succeeded by a considerably augmented flow of urine. The dotted line represents the average blood-pressure at each period. It will be observed that each injection is followed by some increase in the arterial tension. Contrast Fig. 24 (p. 25[illegible]) as to the amount of the secretion, and also as to the behavior of the blood-pressure.

In ~~heart~~ man slow + strong. In some fevers X has lost tone + digit. fails to slow heart. Hence caution in giving increasing doses ~~thinking~~ first hasn't acted. Examine amt of urine, dyspnoea, disappearance of oedema. When heart slow, pulse is full of stronger (heart 2 more complete relaxation + filling of) vessels under finger

abdominal organs (Gottlieb and Magnus). And in accordance with this it has been observed that a larger diuresis sometimes follows from moderate doses than from very large ones. The increased blood stream is due for the most part to the augmented efficiency of the heart and not to the vascular changes, though it is possible that if the renal vessels are less readily contracted than those of the other organs this may serve to divert the blood current to the kidney. It may be supposed that the accumulation of the blood in the arteries and the consequent fall of the venous pressure, which has been shown to occur, lead to an augmented flow of the lymph into the blood vessels, and that the blood is thus diluted and the kidneys therefore incited to abnormal activity, while at the same time their nutrition is improved by the acceleration of the general circulation and possibly by some local dilatation of the renal vessels. It is possible, also, that at any rate some of the members of this series act as slight irritants to the renal epithelium. The appearance of blood and albumin in the urine of animals after large doses of squills and digitalis certainly indicates some local action quite apart from the circulatory changes.

The changes in the circulation in man can be followed only imperfectly. The heart rhythm is very distinctly slower and the apex beat is much stronger than before the administration of the drug; the pulse is slower and stronger and fuller. It must be added that the strength of the pulse is not to be regarded as a gauge of the changes in the cardiac muscle, for it is due not only to the increased strength of the cardiac contraction, but also to its slow rhythm. When the heart is beating rapidly, the arteries have no time to empty themselves completely and the pulse is small, while on the other hand, when digitalis slows the heart, the arteries have time to empty their contents into the capillaries before the next contraction occurs, the walls therefore become more flaccid, and a new wave of blood causes a more distinct impulse. In some cases of fever the vagus seems to have less control over the heart than usual, and after digitalis there is no very marked slowing, although the action on the cardiac muscle may be fully developed. The pulse is fuller, but it is not much slower, and if the physician, judging from the rate of the pulse that the drug has been given in too small quantities, prescribes larger doses, the effects on the heart may be disastrous, as the third stage of irregularity and less perfect action of the heart may be induced. In those cases in which this series seems to have no action on the pulse, the heart and the general condition of the circulation must be very carefully examined before larger quantities are prescribed. If, for example, the urine be found increased, or the œdema is less marked than before, or the breathlessness and the dyspnœa have disappeared, the drug is fulfilling its chief purpose, even though the pulse remains apparently unchanged.

The blood-pressure does not seem to be augmented in man to any extent perceptible by the methods in use for measuring it clinically, and in some instances is distinctly reduced. This is due to the fact

Bp. not raised as vessel constriction [illegible] [illegible] more blood to Vm. center which is then lessened in activity. Accumulative action & poisoning. Uneasiness. anxiety constant [illegible] etc

[illegible] fall in temperature — stim. of heat regulatory center. / Slowly absorbed & remain active / some destroyed

that in man the vaso-constrictor mechanism is much more perfect than in the lower animals, for otherwise the upright posture would be impossible. The blood-pressure is maintained in man by the constant activity of the vaso-constrictor centre, and any change in the amount of blood supplied to this centre alters the degree of constriction in the vessels. When the circulation is slow, the centre is thrown into activity and there is a constriction in the splanchnic area which maintains the blood-pressure. On the other hand, when the circulation is accelerated, as by digitalis, and more blood is supplied to the centre, its activity is lowered and the splanchnic area is widened. The effect of digitalis on the vessels is thus counterbalanced by its indirect effects on the vasomotor centre, and no rise in pressure occurs.

In **Cases of Poisoning** with the digitalis series, the most alarming symptoms arise from the circulatory changes. In the well-known case of Koppe, who accidentally poisoned himself in the course of his investigations on digitoxin, the first symptoms were uneasiness, giddiness, nausea and vomiting and great muscular weakness. The pulse then fell to about half its normal rate and became intermittent, and the increasing muscular weakness was accompanied by precordial anxiety, imperfect vision and constant nausea and vomiting, which prevented sleep and rest, and which persisted for over thirty-six hours without improvement. The symptoms then slowly disappeared and he recovered entirely in about a week. The quantity taken by him was 2 mg. (1/30 gr.), but four days previously he had taken 1 mg. (1/60 gr.), and it is possible that this may not have been absorbed completely. In any case the small dose of digitoxin necessary to induce almost fatal symptoms indicates that it is one of the most powerful poisons known at present.

The main action of this series is on the circulation, but some other results of their administration of less consequence have been observed. Thus in fever the **Temperature** is not infrequently reduced, although it remains unchanged after the administration of digitalis to the normal animal. This action is said by some to be the result of collapse, while others believe it to be due to the changes in the circulation, but neither of these seems to be a very happy explanation. It has been stated already that the members of this series act as stimulants to some parts of the central nervous system, and a possible explanation of their antipyretic action would be an increased activity of the temperature-controlling centre. It has been shown by Harnack that several central nervous stimulants, including picrotoxin, cause a fall in the temperature in this way.

Digitalin and its allies are very slowly **absorbed** from the alimentary tract and a considerable amount of some of them appears to be destroyed in the process. Even after they reach the blood, they seem to affect the heart and vessels more slowly than most drugs. On the other hand, their effects are very prolonged, the heart remaining slow for several days after the drug has been stopped. After repeated doses there is therefore a tendency to increased action or cumulative

Dig. ½-2 gr. ext ⅕ Fl ext 1 m Inf 8 Tinct ½ Digitaline unreliable.
Digitalinum verum OK! for hypo Digalen!
Tinct Stroph .3-1 cc · Strophanthinum $\frac{1}{200}$ gr - unreliable
Scilla .05-.2 G Fl ext .05-.1 cc Syr 2-4 cc Tinct .3-1

action. The glucosides appear to undergo decomposition in the tissues, but traces have been found in the urine.

The digitalis bodies weaken and eventually paralyze the **Muscles** and the terminations of the peripheral **Nerves** of the frog. For this purpose it has to be applied in quantities which would at once stop the mammalian heart, and this action certainly never even commences in warm-blooded animals. Large quantities of digitalis are said to act on the unstriated muscle of several organs, such as the stomach and uterus, and to increase their movements, and this certainly occurs in excised organs exposed to solutions of the glucosides.

Preparations.

Digitalis (U. S. P.), **Digitalis Folia** (B. P.), foxglove, the leaves of Digitalis purpurea collected from plants of the second year's growth. 0.03–0.1 G. (½–2 grs.). .03-.1 G

Extractum Digitalis (U. S. P.), 10 mgs. (⅙ gr.). .010 G

Fluidextractum Digitalis (U. S. P.), 0.05 c.c. (1 min.). .05cc

Infusum Digitalis, U. S. P., 8 c.c. (2 fl. drs.); B. P., 2–4 fl. drs. 8cc

Tinctura Digitalis (U. S. P., B. P.), 0.3–1 c.c. (5–15 mins.). .3-1 cc

"*Digitaline*" of commerce varies much in composition and in dose, sometimes proving entirely inert, while at other times it has proved poisonous in comparatively small quantities. Crystalline digitaline very often consists largely of digitonin, which is quite devoid of the digitalin action. Other preparations seem to contain much digitophyllin. "*Digitalinum verum*" is said to be pure digitalin, and may be injected subcutaneously without danger. 2–6 mg. ($\frac{1}{30}$–$\frac{1}{10}$ gr.).

Digitoxin has been prescribed in doses of $\frac{1}{12}$ mg. ($\frac{1}{780}$ gr.), but the forms at present on the market vary greatly in strength. *Digalen*, or amorphous digitoxin, has been introduced of late years, but does not seem constant in composition, for several investigators have found it altogether inert.

The tincture and infusion are the most commonly used preparations. The extract and the powdered leaves may be given in the form of pills. The preparations ought to be freshly made and solution of "digitaline" and digitoxin must not be kept, as they soon decompose.

Strophanthus (U. S. P.), **Strophanthi Semina** (B. P.), the seeds of Strophanthus Kombé.

Extractum Strophanthi (B. P.), ¼–1 gr.

Tinctura Strophanthi (U. S. P., B. P.), 0.3–1.0 c.c. (5–15 mins.). .3-1 cc

Strophanthinum (U. S. P.), varies in composition and in power. Its dose is given as 0.3 mg. ($\frac{1}{200}$ gr.), but this is often devoid of action, while in other cases 0.2 mg. has been found a sufficient dose, and it is therefore to be used with caution. Its solutions are very liable to decompose and have to be freshly prepared. A "crystalline strophanthin" has been obtained by Thoms from strophanthus gratus and is said to be a definite body with a dose about half of that of the official strophanthin. $\frac{1}{200}$ gr

Scilla (U. S. P., B. P.), squills, the bulb of Urginea maritima, Urginea Scilla, or Scilla maritima, deprived of its dry membranaceous outer scales and cut into thin slices. 0.05–0.2 G. (1–3 grs.) in pills.

Acetum Scillæ (U. S. P., B. P.), 1–2 c.c. (15–30 mins.).

Fluidextractum Scillæ (U. S. P.), 0.05–0.1 c.c. (1–2 mins.).

Tinctura Scillæ (U. S. P., B. P.), 0.3–1 c.c. (5–15 mins.). .3-1 cc

Syrupus Scillæ (U. S. P., B. P.), 2–4 c.c. (30–60 mins.). 2-4 cc

Syrupus Scillæ Compositus (U. S. P.), containing senega and tartar emetic, 2 c.c. (30 mins.).

Oxymel Scillæ (B. P.), ½–1 fl. dr.

Pilula Scillæ Composita (B. P.), contains ginger and ammoniacum, 4–8 grs.

Pilula Ipecacuanhæ cum Scilla (B. P.), contains 5 per cent. opium. 4–8 grs.

[illegible] fullo cough – contains [illegible]

Pills of Squill for diuresis. Standardized & [illegible] necessary to stop frog heart in certain time

[illegible] – dilated weak heart. Venous congestion. Gives increased velocity for better nutrition of body & for heart tending hypertrophy possible then stop drug

Squills is often prescribed in pill form as a diuretic; as an expectorant the syrup is more often used. The compound syrup, U. S. P., or the pill of Ipecac and Squill, B. P., may be ordered instead of a cough mixture, as they contain the chief constituents of such remedies.

Scillotoxin, etc., of commerce are merely purified extracts and not pure principles.

Apocynum (U. S. P.), Canadian hemp, the root of Apocynum cannabinum.

Fluidextractum Apocyni (U. S. P.), 1 c.c. (15 mins.).

Convallaria (U. S. P.), Lily of the Valley, the rhizome and roots of Convallaria majalis, 0.5 G. (7½ grs.).

Fluidextractum Convallariæ (U. S. P.), 0.5 c.c. (8 mins.).

Euonymus (U. S. P.), **Euonymi Cortex** (B. P.), Wahoo, the bark of the roots of Euonymus atropurpureus, 0.5 G. (7½ grs.).

Extractum Euonymi (U. S. P.), 0.125 G. (2 grs.).

Extractum Euonymi Siccum (B. P.), 1–2 grs.

The importance of this group in therapeutics is so great that it is to be regretted that no adequate method of chemically estimating the content of active principles is available. For the crude drugs appear to vary in activity very greatly, and even when the attempt is made to use the glucosides themselves, the difficulty in their isolation and identification leads to uncertainty in their dosage. There has therefore been introduced (Houghton) a method of assaying the strength of the preparations of digitalis, squills and strophanthus according to the quantity necessary to produce changes in the circulation. As a general rule the smallest quantity which is sufficient to arrest the frog's heart in a definite time has been taken as the unit, and such *standardized* preparations are now available. The active principles stand in no less need of being assayed. Only by using these standardized preparations can there be any certainty that the patient is receiving a uniform dose of these drugs (Edmunds).

Therapeutic Uses.—The chief purpose for which this series is used in therapeutics is to counteract certain changes in the circulation, which result in the blood accumulating in the veins in too large quantities, while the arteries are less completely filled than usual. And first of all, in cases of dilatation of the heart with a weak and insufficient systole, its action is almost specific. This is true whether one or both ventricular chambers are affected, as long as the cardiac muscle itself has not undergone degeneration. In these cases the action is very simple—the increased ventricular systole approaches the normal, the output of the heart is increased, and in some cases at any rate, the dilatation is diminished by the direct action of the drug. The effect is an increased velocity and pressure in the arteries, and an improved nutrition of the whole body. The organ which suffers most of all under the malnutrition caused by dilatation of the chambers is the heart itself, and, accordingly, in these cases the heart is found better nourished and has more tendency to hypertrophy after digitalis or its allies. Eventually the walls of the heart become so enlarged as to be able to carry on the work without the additional stimulation of digitalis, and the drug ought therefore to be stopped. It must be remembered that the hypertrophy of the heart is not a

Systole strengthened and output increased. In mitral insufficiency - increased force increases amt of blood to system & tends to tighten valve. Further stronger R. heart overcomes congestion in lungs & R auricle may now be filled. Heart's dil. that overcome valve orifice tends to become closed.

direct effect of this series, which only puts the organ in a condition in which it receives more nourishment and is therefore more likely to hypertrophy. The effects in these cases of dilatation seem to be attributable entirely to the action on the cardiac muscle.

It is frequently stated that the slowing of the heart, which allows the heart more time to rest and more time to fill itself, is accountable for the improvement. But numerous other drugs slow the heart quite as much and in exactly the same way, yet are of no benefit, but rather the reverse in those conditions in which digitalis is most valuable. Aconitine, for example, slows the heart by stimulating the vagus centre, but no one would dream of using aconite as a substitute for digitalis in dilatation of the ventricles. The true explanation of the action of digitalis is the action on the cardiac muscle, by which the systole is strengthened and the output of the heart is increased.

Mitral incompetency may be taken as a concrete example of cardiac disease. Here some of the blood, instead of passing into the aorta during the ventricular systole, passes back into the auricle. The efficiency of the heart is thus reduced and the blood tends to accumulate on the venous side and the nutrition of the whole body suffers. This leads to dilatation of the heart chambers and congestion of the lungs. Œdema and dropsy follow, the kidneys and other organs become overfilled with blood, and the whole economy is thrown into disorder. If now one of this series be given, the right and left ventricles commence to beat more strongly, their output is increased, and the blood is forced through the lungs. It still regurgitates into the left auricle, but the proportion passing back to that driven forward is smaller, owing to the increase in systole, which lessens the mitral orifice. Moreover the right ventricle is able to overcome the pressure in the pulmonary artery, and therefore soon ceases to drive blood into the right auricle, and the systemic veins can pass their blood into the heart without difficulty. The congestion of the organs rapidly disappears, the kidneys become better nourished and secrete rapidly, thus draining off the large quantities of fluid accumulated in the body. The heart itself improves in condition, but more work is required of it than in the normal body, because some of its work is still lost through the blood passing backwards from the ventricle instead of forwards. The muscle responds to the strain by hypertrophy, and when this process is complete, the drugs have fulfilled their purpose, and further administration is useless and may be dangerous.

The only action of the drug required here is the increased contraction of the ventricles and auricles in systole, and this is exactly the point in which this series differs from all others. At the same time, if the diastolic dilatation becomes less marked, as it does in many experiments on the normal heart, this must also aid in such a case, because the more dilated the ventricle the less perfectly does the mitral valve close the auriculo-ventricular orifice at the beginning of systole. If then the dilatation of the heart becomes less, either from a direct action of the drug, or as a result of the improved nutrition of the muscle, the imperfection of the valve may be compensated for by the auricles + papillary muscles [illegible] [illegible]. In aortic regurg. more out, in diastole counteracts longer time for regurg. In stenosis to abolish regurg effects. In pulmon. disease to force thru lung

narrowing of the orifice. If the muscular action predominates sufficiently over the inhibitory, a further factor may aid in repairing the breach of the valve, for the auricular muscle is acted on in the same way as the ventricular—its contraction is more complete, and the auricle therefore empties itself more perfectly and contains less blood at the beginning of the ventricular systole than it otherwise would. If, in addition, the auricular relaxation is lessened by digitalis, a greater resistance must be offered to the regurgitating blood. The increased contraction of the papillary muscles may also aid in the therapeutic effect by closing the valves more completely.

In aortic incompetency the same beneficial results may be expected, because here again there is more blood expelled into the aorta. The less dilated ventricle also presents a greater resistance to the return of the blood. It is true that longer time is allowed for the blood to pass back into the ventricle owing to the prolongation of the diastolic pause, but this does not seem to be sufficient to counterbalance the benefits of the more complete contraction of the ventricle. In experimental lesions of the aortic valves in animals digitalis is found to improve the efficiency of the heart, and a smaller mortality occurs in animals under treatment than in the controls.

In narrowing of the orifices, the improvement observed after digitalis may also be explained by the stronger and more complete contraction of the ventricles. Stenosis very rarely occurs unaccompanied by regurgitation, however, and the diminution of the backward flow may be the main object attained by these drugs in this condition.

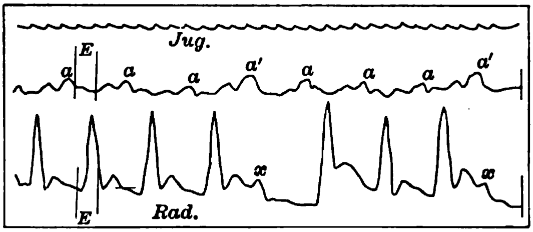
On the right side of the heart the same action occurs as on the left, and in dilatation of the right ventricle, which often occurs as the result of pulmonary disease, this series acts by increasing the strength of the ventricular contraction.

Irregularity of the heart often disappears under digitalis treatment, apparently in many cases from the improvement of the cardiac nutrition. In other forms the vagus stimulation may perhaps lessen the tendency to irregularity, but this requires further investigation. On the other hand, the use of digitalis sometimes gives rise to irregularities and the character of these has received a good deal of attention of late years. The first form arises from the muscular action which may increase the excitability of the ventricle or auricle so much in some cases that spontaneous beats (extrasystoles) may arise (Fig. 49). These are not of great importance, but the heart should be carefully watched and, if possible, the dose should be reduced. Other forms arise from the stimulation of the inhibitory mechanism. Thus when the pulse is very much slowed, the intervals between the beats are often variable and the powerful contractions cause an unpleasant sensation in the chest. This occurs when the vagus is strongly stimulated from any cause and is not peculiar to digitalis. When this form of irregularity sets in the dose should be reduced or the drug omitted altogether for a few days. Not infrequently a less obvious vagus effect causes irregularity under digitalis. When the conduc-

Lessens some irregularities by x stim. of by better nutrition.
Causes " " by depression of bundle of His or vict. Jaundice
May lead to complete heart block

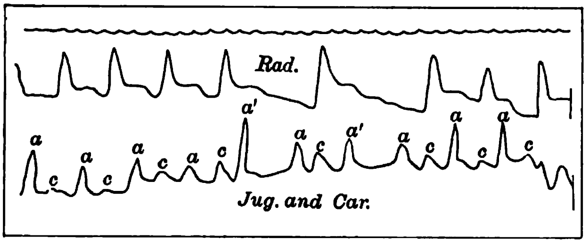
tion from the auricle to the ventricle is slightly impaired by disease, it is found that digitalis accentuates the weakness. Before the treatment the fibres were able to conduct all the impulses from the auricle to the ventricle, though perhaps they passed more slowly than in quite normal hearts. But now an occasional impulse fails to pass, or perhaps only one of two impulses passes to the ventricle. When an impulse fails to reach it the ventricle remains in diastole (dropped beat) (Fig. 50), and when only one-half the impulses pass to it, the rhythm of the ventricle is only half that of the auricle (half rhythm) (Fig. 51). Or the block may be complete, no impulses passing

FIG. 49.



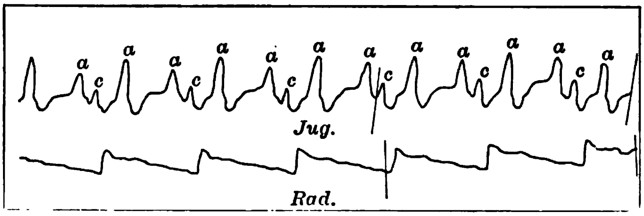
Shows a jugular pulse of the auricular type with the occasional occurrence of a ventricular extra-systole. The auricular waves (*a* and *a'*) occur at regular intervals, while the small waves (*x*) in the radial occur prematurely. The larger size of *a'* is due to the fact that when the auricle contracts the ventricle is already in systole, and therefore cannot receive the auricular contents, which are thus sent back into the veins, producing this larger wave. (MACKENZIE.)

FIG. 50.



Tracings of the radial (upper) taken at the same time as the jugular and carotid. The waves *a* and *a'* are due to the auricle, and appear with perfect regularity, while the radial pulse and carotid (wave *c*) appear irregularly—a beat missing after each auricular wave *a'*. (MACKENZIE.)

FIG. 51.

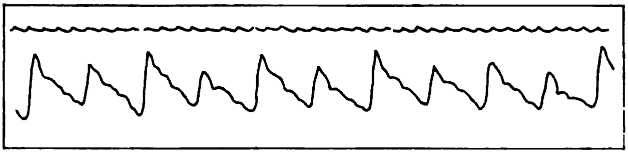


Slowing of the pulse due to digitalis depressing conductivity, so that the ventricle fails to respond to every second stimulus from the auricle. While the ventricle contracted 48 times per minute, the auricle contracted 96 times. (MACKENZIE.)

Pulsus alternans in radial irregularities [illegible] - impaired contractility
Fever = dil + poor contraction - fluttering pulse - fast rate } give dig.
Ditto pneumonia + pulm. obstruction.

through the fibres at all and in this case the ventricle takes up its own spontaneous rhythm (heart-block). Digitalis causes the failure of impulses because the inhibitory mechanism which it stimulates lessens the conductivity of the fibres. This form of irregularity is therefore quite apart from the muscular action; but it is generally necessary to abandon digitalis treatment when it gives rise to lessened conduction, at any rate in its more aggravated forms. Another form of irregularity which sometimes appears under digitalis is known as *pulsus alternans* (Fig. 52), and is marked by an alternation of strong and weak beats of the radial pulse. This generally indicates impaired contractility of the ventricular wall, and its occurrence under digitalis has not as yet received adequate explanation.

FIG. 52.



Typical pulsus alternans due to digitalis. Each pulse period is of the same duration, while the size of the beat varies rhythmically. (MACKENZIE.)

In numerous acute febrile conditions the heart becomes affected, possibly in part by the high temperature, but largely from the toxic products circulating in the blood. The chief cardiac symptoms are dilatation with a weak systole and a small "fluttering" pulse. In these cases digitalis and other similar drugs may be of great service in slowing the accelerated heart and in increasing the extent of systole, and thus improving the general circulation. In pneumonia more especially great improvement is often seen after digitalis. In this disease, besides the toxic action on the heart there may be present more or less obstruction of the pulmonary vessels through pressure, resulting in overwork and dilatation of the right heart. The routine treatment of pneumonia with digitalis is often recommended, but is to be deprecated on the general principle that a drug is not to be prescribed until some special indication for it appears; unless distinct evidence of circulatory disturbance is present, digitalis ought to be withheld.

In acute fevers the inhibitory mechanism is often less irritable than normally, and the activity of the drug must not be estimated by the slowness of the pulse. (See page 373.)

In some forms of dilatation of the heart digitalis and its allies are to be avoided. Thus where extensive degeneration of the heart muscle is present, as in fatty heart, little or no benefit from the muscular action is to be expected, for the muscle itself is too weak to respond to the stimulation. On the other hand, digitalis may cause the most serious results—the systole becomes even weaker than before its administration, and brain anæmia, syncope and not infrequently

Contraind: in diseased myocard. + in vessel disease – then give a vessel dilator – nitrites (frequent small doses)
O.K. in some high b.p.s. as here a v.const. cnd. to maintain supply to brain
Dig. esp for uncompensated valvular lesions + hypertr

sudden death follow. In other cases, while the condition of the heart is eminently suitable for digitalis treatment, disease of other parts of the body may preclude its use. Thus if extensive degeneration of the arterial coats is present, digitalis incautiously used may lead to rupture of their walls and apoplexy. In those cases strophanthus is generally preferred to digitalis, and it is recommended that either be prescribed along with some drug to dilate the vessels and lessen the arterial tension, such as nitroglycerin or some other of the nitrite series. In treating with digitalis and a member of the nitrite series it is found that the digitalis action sets in somewhat slowly and persists for a long time, while the nitrites act rapidly, but are excreted comparatively soon. The best results are therefore obtained by frequent small doses of nitroglycerin, which need not be administered for some hours after the first dose of digitalis.

In some cases dilatation of the heart seems to be due, at any rate in part, to increased arterial tension from disease of the arterial walls and of the kidneys. In these cases digitalis is to be used with caution, and perhaps strophanthus is to be preferred to digitalis, unless one of the nitrite series is associated with the latter. A high blood-pressure ought not to be regarded as definitely contra-indicating the use of digitalis or its allies, however, for excellent results often follow its exhibition in these cases, provided the special indications for digitalis are presented in venous stasis, œdema or deficient urine. In these cases the high pressure presumably arises from excessive activity of the vaso-constrictor centre inducing mesenteric constriction in an attempt to maintain the blood supply to the brain; this involves an abnormal resistance to the circulation and imperfect nutrition of various organs. Digitalis by increasing the efficiency of the heart improves the blood supply of the brain and the activity of the vaso-constrictor centre is abated, leading to a more normal state of the circulation and often to a lower arterial tension.

Valvular disease is not in itself an indication for digitalis, for the heart tends to undergo compensatory hypertrophy in favorable conditions without the use of any drug whatever, and digitalis is indicated only when no such compensation occurs. At the same time hypertrophy of the heart is not a contra-indication, as is often stated, for a special strain may cause excessive dilatation in a hypertrophied heart, and digitalis may be necessary until a second hypertrophy has occurred and restored the equilibrium once more.

Digitalis is often prescribed in tachycardia (rapid heart) in order to slow the rhythm only, but if no other symptoms than acceleration are present, other drugs, such as aconite or strychnine, may be substituted for digitalis, and do not entail the other changes in the circulation.

It has been mentioned that the exhibition of digitalis in fever is often followed by a fall of temperature, and Traube recommended it as an antipyretic, but it is no longer used for this purpose, as the modern antipyretics are much more powerful and certain in their action, and at the same time are less dangerous.

Other drugs preferable as antipyretics + diuretics (unless comb. with heart [illegible]. Then squills + digit + calomel. In bronchitis squills better r. heart (due to cough) & [illegible] nausea increases secretion (as ipecac)

Is better use in emergencies (as loss fm [illegible]) give hypo? stroph $\frac{1}{500}$ – $\frac{1}{60}$ gr

The diuretic action of digitalis is also not advised except where other indications than a diminution of the renal secretion are present, for in ordinary cases it has much less effect than caffeine and other diuretics. If the anuria be secondary to disturbances of the circulation, however, digitalis is the diuretic par excellence and cannot be replaced by any of the ordinary means of promoting the urinary secretion, although they may advantageously be combined with it. Squills is more frequently used as a diuretic than digitalis, and it seems probable that in addition to its action on the heart and circulation, it exercises some direct stimulant influence on the renal epithelium. Squills and digitalis are often prescribed together, where large accumulations of fluid have to be removed. A famous pill used in these cases contains a grain each of digitalis, squills and calomel.

Several of these drugs are of considerable benefit in pulmonary diseases accompanied by cough. Thus in bronchitis, more especially in cases of old standing, the addition of squills to an "expectorant mixture" is often followed by the most satisfactory results. The action here is probably two-fold. In the first place, the right heart may be dilated owing to the frequent strain put on it by coughing, and squills remedies this condition by its usual cardiac action. In the second place, all these drugs possess to a certain extent emetic properties, and thus cause an increase in the bronchial secretion, and render the sputum less tenacious and more easily expectorated. The addition of squills, in which this property is more developed than in the others, has the same effect as the prescription of ipecacuanha, along with the further action on the heart.

Digitalis is sometimes prescribed to stop hæmorrhages, but even when it constricts the vessels it accelerates the flow through them, and, as in the case of other hæmostatics, the benefits arising from the treatment are problematical. In the circulatory weakness following severe hæmorrhage and shock the effects of this series would seem to be indicated, were it possible to elicit their action sufficiently rapidly. Unfortunately many hours generally elapse before the heart and vessels are affected, when they are exhibited by the mouth. These conditions are generally treated by more rapidly acting measures, such as the intravenous injection of salt solution; the effects of this treatment are maintained much longer if a small quantity of digitalis tincture is added to the salt solution. The injection of strophanthin intravenously in doses of ½–1 mg. (1/120–1/60 gr.) has been advocated recently in emergency cases; this dose must not be repeated within twenty-four hours.

Squills was at one time used as an emetic, but this cannot be recommended, owing to the danger of its absorption. Euonymus has been employed as a purgative more frequently than as a cardiac remedy.

Some conditions in which the cardiac action of this series is to be elicited only with the greatest caution, have already been indicated. A further danger, which attends the use of digitalis perhaps more than that of the rest of the series, is due to its **Cumulative Action.**

Great accumulative action. None till 2 day. (Sy = ~~ft~~ bradycardia irregularity, vomiting etc. to discontinue at once. Acts some time. Esp digitoxin. Some of the "pure principles" (tho unreliable) cause less g. irritation.

For the first day or two after the exhibition of this drug no effects may be noted in the pulse or general circulation; the ordinary symptoms are then produced, and if the drug be continued, remain fairly constant for some time. Sometimes much more marked symptoms of digitalis action appear suddenly, however,—the pulse becomes alarmingly slow and irregular, the patient complains of weakness and faintness, nausea and occasionally vomiting, in fact the symptoms of the second stage set in. This is known as cumulative action, and is probably due to irregularities in the absorption and excretion or destruction of the poison. It is known that the absorption is slow, for 12–36 hours may elapse before any effects follow the exhibition of the drug. On the other hand, the excretion or destruction must be equally slow, for the symptoms sometimes last for several days after it has been discontinued. If then anything happens to disturb the equilibrium of absorption and excretion, if, for example, the excretion is slower than usual, or if any irritation of the stomach and intestines causes a more rapid absorption, the drug accumulates in the blood, and the same effect is produced as if a poisonous dose had been administered. In order to avoid this cumulative effect, the condition of the pulse must be carefully controlled, and as soon as the circulation shows any signs of excessive action, the drug ought to be discontinued for one or two days and resumed in smaller quantities. These cases of poisoning are not serious if observed in time. All of the digitalis series hitherto examined prove to be cumulative in their action, but some of them, notably digitoxin, are much more dangerous than others. In fact, according to Fraenkel, digitoxin can only be used safely in doses which induce no changes in the pulse for several days, for if the pulse be slowed by a single dose, its repetition within twenty-four hours induces severe poisoning.

Another disagreeable feature observed in the use of this series is the action on the stomach and intestine. As has been noted already, the local action may produce the usual symptoms of gastric irritation, and the patient suffers from loss of appetite, nausea and gastric discomfort, just when it is important that the nutrition should be the best attainable. Numerous attempts have therefore been made to obtain preparations which possess the cardiac without the local action. Some of these seem to be fairly free from irritant properties; for example, some of the digitalines can even be injected subcutaneously without giving rise to any irritation or inflammation. But unfortunately all those preparations vary so much in strength, even when prepared by the same method, that their use is scarcely to be recommended. At the same time, in cases where the ordinary pharmacopœial preparations cause marked gastric irritation, some of the so-called "pure principles" may be made use of with advantage.

So little is known regarding the comparative action of the members of this series that the special indications for each individual are altogether indefinite. It is recognized that strophanthus acts less on the vessels than digitalis, and this gives an indication for its use in

Stroph. - Less action on vessels · Squills = better diuresis & expectoration ·

some cases. On the other hand, squills acts more on the kidney than either, and is therefore given frequently as an adjuvant to digitalis in cases where diuresis is desired. It also irritates the gastric mucous membrane more, and is often used as an expectorant. But the details of the action of each are still to be worked out. One important question, which is practically unbroken ground, is the relative action of each on the vagus centre and on the heart. The beneficial results from the use of digitalis are, as has been pointed out already, to be ascribed almost entirely to its action on the cardiac muscle. The stimulation of the vagus may conceivably lessen the benefits of the cardiac action by weakening the auricular contraction and slowing the rhythm, so that it would be of considerable interest and importance to find a drug having the same cardiac action without the inhibitory,[1] and, failing in this, to compare the effects of digitalis alone with those of digitalis and a drug which weakens the inhibitory action. This would have to be given in quantities sufficient to prevent an increased inhibition without cutting off the normal restraining impulses which pass down the vagi, and the treatment would be rendered considerably more difficult.

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[1] Helleborein has comparatively little action on the inhibition, but in a number of cases of cardiac disease in which I have attempted to substitute it for digitalis it induced irritation of the intestine and diarrhœa through its local irritant action.

Large dose = death. Heart & CNS failure. Smaller dose. Bitter. Tingling on m
stomach & skin - [illegible]. maybe vomiting salivation. slow pulse & deep resp
weakness. consciousness till end. After tingling = anaesthesia
also veratrine

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XXI. ACONITINE.

This series embraces a number of alkaloids, which resemble each other so closely in their chemical and pharmacological properties as to allow of their being treated together. Some of them which were formerly believed to be perfectly distinct are now said to be identical, and it is not improbable that future investigation will still further reduce the numbers of the group.

These alkaloids are found in a number of species of the Aconitum genus, the best known of which are Aconitum Napellus, containing *Aconitine* ($C_{33}H_{45}NO_{12}$ or $C_{34}H_{47}NO_{11}$), Aconitum ferox, *Pseudaconitine* ($C_{36}H_{49}NO_{12}$), and Aconitum Japonicum, *Japaconitine* ($C_{34}H_{49}NO_{11}$).

When aqueous solutions of these alkaloids are heated, they are broken up into one or more acids and simpler bases, so that they may be classed with those of the atropine and cocaine series, which are similarly decomposed. Aconitine forms acetic acid and *Benzaconine* (or picroaconitine), which may again be broken down into benzoic acid and *Aconine,* so that aconitine is acetyl-benzoyl-aconine. Pseudaconitine forms *Pseudaconine,* and Japaconitine *Japaconine* in the same way. These decomposition products are found in the plant and in the ordinary preparations, and in many of the commercial "aconitines" benzaconine and aconine occur in varying proportions, so that their toxicity varies very considerably.

Another alkaloid which resembles aconitine closely in its pharmacological action, but which is less known, is *Delphinine.* It is found in stavesacre (Delphinium Staphisagria), along with a number of other bases, which may be the products of its decomposition.

The symptoms caused by aconitine, pseudaconitine, japaconitine and delphinine are very similar, differing mainly in degree and not in kind. Pseudaconitine is more poisonous than japaconitine which in turn is slightly more active than aconitine. Delphinine is much less poisonous.

Symptoms.—After very large quantities of aconitine death may result instantaneously, apparently from simultaneous failure of the heart and central nervous system.

If smaller quantities be swallowed there is noted, after the ordinary bitter taste of the alkaloid, a feeling of warmth in the mouth and throat, which, agreeable at first, soon becomes prickling and tingling, and extends to the stomach and eventually to the skin. This is accompanied by a profuse flow of saliva and often by vomiting. The pulse is very slow and may be irregular, and later becomes weak and imperceptible, when symptoms of collapse appear. The respiration is slow and labored, and great muscular weakness is complained of. After a time the smarting and tingling of the skin are no longer felt, and on examination the cutaneous sensibility is found to be much reduced. The intelligence remains unimpaired to the last in many cases, although unconsciousness sometimes occurs, and death is gener-

Small dose = slows heart tingling of lips tongue throat. On nerve ends also of locally. Heart stim. [illegible] & [illegible]. [illegible] in conduction. Like digitalis. Large doses only slows pulse - so low BP [illegible].

ally, but not invariably, preceded by convulsions. The pupil is unaffected except when convulsions supervene, when it is dilated. The prickling of the throat and skin is the most characteristic symptom, and is practically diagnostic in cases of poisoning, no other drug excepting veratrine having this effect. Death is due to paralysis of the respiratory centre from the direct action of the poison, although this may be aided by anæmia of the medulla from the imperfect circulation.

In small doses aconitine induces slowing of the heart and slight muscular weakness, which is often accompanied by tingling of the lips, tongue and throat.

Action.—The prickling, tingling sensation is due to an affection of the **Terminal Organs of the Sensory Nerves,** as is shown by its appearing first at the point of application of the drug. Thus, when aconitine is swallowed the prickling and warmth is felt in the lips, tongue and throat, and after small doses may be confined to these parts, while if an ointment containing aconitine be rubbed on the skin, the same sensation is induced locally. But no redness or swelling of the skin is induced, nor are blisters formed, so that aconitine differs entirely from the class of skin irritants (page 81). It evidently acts by stimulating the terminations of the sensory nerves, more especially those of common sensation, while the other sensory end organs have not been shown to be involved. Thus, apart from the bitter taste which it possesses in common with all alkaloids, aconitine has no effect upon the taste organs during this stage. The stimulation afterwards passes into depression, which induces a sense of numbness at the point of application, and in cases of poisoning, in all the surfaces of the body. The taste nerves seem to be involved in this effect, if Laborde's statement be correct that sweet substances have no taste after aconitine. The irritation of the sensory terminations often causes a number of reflexes, such as sneezing, coughing, increased secretion of saliva and vomiting, although some of these may be due in part to stimulation of the medullary centres. Evidence of the stimulation of **Other Terminations** is presented in fibrillary twitching of the muscles in the frog and sometimes in mammals. This is prevented by curara, but not by section of the nerves, and is therefore attributed to stimulation of the terminations of the motor nerves in muscles.

The effects of aconitine on the **Circulation** are somewhat complex, as the heart is affected directly by it, as well as through its inhibitory nerves, and the vasomotor centre is stimulated in addition. The frog's heart is first accelerated from the direct action of the poison, but this soon passes into the slow pulse and prolonged diastole which are characteristic of inhibitory action. The subsequent standstill may at first be removed by atropine, but somewhat later this remedy fails, as the drug begins to act directly on the heart. A second acceleration may be thus induced, but the contractions soon become irregular and groups of almost normal beats alternate with peristaltic movements which fail to expel any blood from the heart. Later, the large contractions may alternate with periods of complete quiescence in the ventricle, while the auricles continue to beat, and stimulation of the accelerans nerve is followed by periods of regular contraction. The heart muscle seems to have lost in great part its power of conducting impulses, so that the contraction of the auricle often fails to excite a ventricular systole; but if the conductivity be increased by stimulation of the accelerator nerve, or if the ventricle be excited by a series of electric shocks, it responds by rhythmical contractions.

In mammals the preliminary quickening of the heart is masked by the strong stimulation of the vagus centre. This produces marked slowing of the pulse, an increased dilatation in diastole and a powerful systolic contraction; the amount of blood leaving the heart is considerably reduced and the circulation is slackened. These symptoms are the only ones seen in the heart except with very large doses of the drug. They are shown to be due to the action on the inhibitory centres in the medulla by the fact that section of the vagus brings the heart back to its normal rate and extent of contraction. In medicinal doses, then, the only effect of aconitine on the heart is due to the vagus stimulation, the direct cardiac action not coming into play, and the administration of aconite in therapeutics is one of the best methods of eliciting pure and unmixed inhibition.

In fatal doses aconitine exerts a further action on the heart, however, for the direct muscular action now comes into play and the heart suddenly accelerates from the slow vagus rhythm to one far above the normal. Soon irregularities follow of many different forms, one of the most common being reversal of the beat, in which the ventricle contracts before the auricle and gives the rhythm to the heart. Eventually the heart passes into fibrillation. The acceleration is due in part to the paralysis of the inhibitory mechanism, but this is insufficient to explain it wholly; there is in addition a marked augmentation of the irritability of the cardiac muscle accompanied by weakened contractility and conduction. These changes arise from direct action on the heart muscle, but there is no reason to suppose that they are induced by therapeutic doses. After section or paralysis of the vagus, a much larger quantity of aconitine is required to produce the acceleration and final delirium than when the nerves are intact.

The blood-pressure in mammals falls rapidly from the lessened output of the heart in the stage of vagus stimulation. There is some evidence of an action on some part of the vasomotor mechanism as well, for some observers have noted a rise in arterial pressure after aconitine in animals in which the vagi had been divided or paralyzed before the exhibition of the drug. The fact that the vagus centre is so strongly stimulated would also suggest the probability of some increase in the activity of the vasomotor area. After the stage of acceleration has set in, the blood-pressure becomes extremely irregular, alternately sinking to zero and remaining at that point for some seconds and again attaining a fair height. These variations are evidently due to the alternations in the heart's movements. The vaso-

Slow labored. Resp. – action on center. Usually convulsions & paralysis. V.m. + vomiting centers may be stimulated.

motor centre seems eventually to become paralyzed, for it has been found that stimulation of an afferent nerve produced no change in the tension, while stimulation of the efferent vasomotor nerves still caused a marked increase. The vasomotor nerves and their terminations in the periphery seem to be unaffected by this poison.

The **Respiration** is early affected by aconitine; it becomes much slower, the movements are more labored than normally, and the animal suffers from marked dyspnœa. The accessory respiratory muscles contract vigorously, and the movements of the abdominal expiratory muscles are so powerful as to suggest the movements of vomiting rather than of respiration. In fatal cases the respiration soon becomes interrupted by convulsions, and in the intervals between these becomes weaker and eventually ceases. Various explanations of the respiratory phenomena have been given. It is certainly not due to action on the phrenic terminations, for the diaphragm contracts on electrical stimulation of these nerves after its spontaneous movements have ceased. The dyspnœa resembles somewhat that seen on stimulation of the centripetal fibres of the vagus, and the theory has been propounded that aconitine stimulates the vagus terminations in the lungs in the same way as the sensory terminations in the skin. The same dyspnœa is seen, however, when aconite is given after section of the vagi, so that it seems to be due to some action on the respiratory centre.

The action of aconitine on the **Central Nervous System** is still a matter of dispute, as the effects on the peripheral nerve-ends tend to obscure the symptoms, but there can be no doubt that certain parts are stimulated. Thus, the vagus centre is undoubtedly thrown into a condition of increased irritability, for inhibition of the heart is a marked feature of the action. Probably the vaso-constrictor centre also undergoes some stimulation, and the vomiting so often seen may be caused, at least in part, by increased irritability of the medullary centres. The convulsions seen in both cold- and warm-blooded animals also point to central stimulation, and the respiratory symptoms are certainly of central origin, though their explanation is still unknown. The higher centres seem to be almost unaffected by the drug, for consciousness has often remained to the end, and when this is not the case, the mental symptoms are to be ascribed to the changes in the heart and respiration. The stimulation produced by aconitine is therefore confined to some of the lower divisions of the central nervous system—more particularly to the medulla oblongata. Some authors suppose that the paralyzing action which succeeds the stimulation is more marked in the sensory than in the motor sphere and as evidence of this it has been pointed out that in frogs the reflexes disappear before the voluntary movements, but this is explained by the anæsthetic action of aconitine on the skin and cannot be accepted as evidence. The paralysis advances much more rapidly in the respiratory centre than elsewhere and death occurs from asphyxia, while the

Sensory stimulation = salivation. Antidote is atropine - stim centers & depresses endings in lung + heart. Excreted by urine

rest of the central nervous system is shown to be still irritable by the occurrence of convulsions.

The muscular weakness often complained of after comparatively small quantities may be due to the depression of the circulation through the inhibitory action, or to nausea.

The **Secretion** of saliva is greatly increased by aconitine from the irritation of the sensory terminations in the mouth and from the nausea. The cold perspiration observed in poisoning may be ascribed to the collapse rather than to any direct action on the sweat glands, although Aubert states that aconitine is a powerful diaphoretic in itself.

Aconitine causes a marked fall of **Temperature** both in fever and in normal animals, but the precise way in which this action is elicited is unknown. Brunton and Cash found that after aconite the temperature fell more rapidly than usual if the animal was kept in a cool bath, but rose more readily if it was subjected to external warmth. The fall in temperature is generally ascribed to the depression of the circulation from the inhibitory action, but this observation would seem to indicate that aconite also acts upon the centres regulating the temperature of the body.

In cases of **Poisoning** in animals atropine has been found to alleviate the symptoms and not infrequently to lead to recovery after doses which would otherwise have been fatal. This improvement is more especially marked in the respiration which may resume its normal character and persist until heart paralysis sets in. Boehm explained this by a supposed action on the terminations of the vagus in the lung, but it is more probably to be ascribed to the stimulant action of atropine on the respiratory centre. In those cases the cause of death is said to be cardiac paralysis, but the stage of irregularity and the final delirium cordis is certainly retarded very considerably by atropine. Atropine appears to be the antidote from which most is to be hoped for in cases of aconite poisoning.

Aconitine is **Excreted** mainly by the urine. Minute quantities have also been found in the saliva and bile.

Benzaconine is very much less poisonous than aconitine and, in fact, can scarcely be included among active poisons, though very large quantities act on the heart, slowing it and rendering it irregular, and also depress the respiration. It has no effect on the sensory terminations. **Aconine** itself is almost inactive, but large quantities strengthen the heart beat and paralyze the terminations of the motor nerves like curara. It seems unlikely that these alkaloids have any influence on the action of the aconite preparations, although the possibility cannot be excluded at present.

The alkaloids obtained from some other species of Aconitum have been found to differ considerably from aconitine and pseudaconitine in their action. In Aconitum septentrionale three bases *lappaconitine, septentrionaline* and *cynoctonine* have been discovered. Lappaconitine causes clonic convulsions, vomiting, dyspnœa and finally paralysis of the respiration and heart, and in the frog lessens the sensibility of the skin. Septentrionaline does not cause poisoning when taken internally, but injected subcutaneously induces local anæsthesia and later paralysis of the motor terminations like curara. Cynoc-

To slow current & heart & bp. (digitalis raises art'l tension) In fever with quick pulse (if heart not weak) give to slow heart & to lower temp. Antipyretics. Locally for neuralgia

tonine is also inactive when swallowed and is less poisonous than the others when applied by hypodermic injection, when it causes tonic and clonic convulsions which are not generally followed by paralysis. Two alkaloids, *lycaconitine* and *myoctonine,* have been found in Aconitum lycoctonum, and induce almost identical symptoms. They increase the reflex excitability, and this is followed by convulsions and later by paralysis of the terminations of the motor nerves and by failure of the heart.

PREPARATIONS.

Aconitum (U. S. P.), **Aconiti Radix** (B. P.), the root of Aconitum Napellus, monk's-hood, containing 0.5 per cent. of aconitine.

8 m .5cc. TINCTURA ACONITI (U. S. P.), 0.045 per cent.; dose, 0.6 c.c. (8 mins.).

TINCTURA ACONITI (B. P.), 5–15 mins. If frequently repeated, 2–5 mins.

Fluidextractum Aconiti (U. S. P.), (0.4 per cent.), 0.05 c.c. (1 min.).

Linimentum Aconiti (B. P.).

Aconitina (U. S. P., B. P.), an alkaloid obtained from aconite root. Commercial aconitine very often contains large amounts of aconine and benzaconine, and therefore varies considerably in activity. Dose 0.15 mg. ($\frac{1}{400}$ gr.). gr 1/400

Unguentum Aconitinæ (B. P.), 2 per cent.

Staphisagria (U. S. P.), **Staphisagriæ Semina** (B. P.), the dried ripe seeds of Delphinium staphisagria, stavesacre.

Therapeutic Uses.—Aconite is employed to a considerable extent in England, the United States and France, while it has fallen into disuse in some other countries. Its pharmacological action suggests its use to slow and weaken the heart and circulation, to lower the temperature and to benumb the terminations of the sensory nerves in the skin. Digitalis is often prescribed to slow the pulse, but it has other effects on the heart and circulation, and where these are not indicated aconite may well be used. Both drugs slow the pulse in the same way, but while aconite slackens the circulation and lowers the blood-pressure, digitalis accelerates the blood current and increases the arterial tension.

The temperature is also reduced by aconite, but the newer antipyretics have supplanted it for this purpose, as they are more certain and more powerful in their effects. The tincture is still prescribed, however, and ought to be given in small repeated doses. When fever is attended by a very quick pulse, aconite is especially likely to be of service, but it ought to be avoided when the heart is very weak.

The action of aconitine on the sensory nerve terminations has been taken advantage of in cases of neuralgia, and there is decidedly much more reason for its use than for that of the great majority of drugs reputed to be beneficial in this condition. Either the tincture, or a 2 per cent. solution of the alkaloid in oil, or the ointment of the B. P. may be employed externally. Aconitine has also been injected subcutaneously ($\frac{1}{100}$–$\frac{1}{10}$ mg.) in neuralgia, but this mode of application is not to be recommended, as it causes very severe pain, which in some cases lasts a long time. The internal administration of aconite in neuralgia does not seem to be followed by any improvement. Stavesacre is scarcely used in medicine at present.

Like aconitine on sensory nerves & CNS. Tingling, nausea, vomit salivation. Often purge

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XXII. VERATRINE.

Several species of the genus Veratrum have been found to contain alkaloids, the most important of which resemble each other in many respects, and also present many points of analogy to those of the preceding group.

The chief members of this series are *Veratrine* (cevadine) and *Protoveratrine,* the former of which is found in Veratrum Sabadilla (Asagræa officinalis or Schœnocaulon officinale), cevadilla, and in Veratrum viride, Green Hellebore,[1] while the latter is the chief active principle of Veratrum album, White Hellebore.[1]

Each of these alkaloids is accompanied by a number of others, most of which are entirely inactive, while several of them are only weak poisons and possess little interest. In cevadilla, in addition to *Veratrine,* there are found *Cevadilline, Sabadine, Sabadinine* and another base, which is known as the *Veratrine of Wright or Couerbe.* In white hellebore *Protoveratrine* is accompanied by *Jervine, Pseudojervine, Rubijervine, Protoveratridine* and others. Green hellebore contains a little *Veratrine* along with *Jervine, Pseudojervine* and *Rubijervine.* Jervine, Sabadine and Sabadinine are known to possess some action on the organism; cevadilline and Wright's veratrine have not been examined, while the others are said to be inactive.

Veratrine ($C_{32}H_{49}NO_9$) and protoveratrine ($C_{32}H_{51}NO_{11}$) are both powerful alkaloids, the latter almost rivaling aconitine in its toxicity. Veratrine can be decomposed into angelic acid and a base, cevine, which seems to be nearly related to aconine. Protoveratrine is probably a combination of isobutyric acid and a similar base. Veratrine occurs in two forms, one crystalline, the other amorphous; the one passes easily into the other, and their effects are ~~identical in animals~~.

The effects of veratrine on the central nervous system and the sensory terminations resemble those of aconitine very closely. On the other hand the muscles present a curious reaction to veratrine, which is entirely absent in aconitine poisoning.

Symptoms.—The symptoms in man and other mammals commence with prickling and burning in the mouth followed by a sensation of warmth in the stomach, marked salivation, nausea and vomiting. The bowel is more involved in the effects than is the case in aconitine poisoning, for violent purging accompanied by severe colic is a common symptom. The prickling sensation soon spreads from the mouth

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[1] Hellebore is also the popular name of Helleborus niger, which differs entirely from Veratrum in its principles and also in its action.

Pulse slow & irregular: Resp slow & labored. On m.m. the sensory stim = sneezing. Vomiting mostly central. Action on striped muscle – incoordination as relaxation is prolonged. [illegible] action of muscle stimulated repeatedly.

5-10 sec

and throat to the skin, and is generally followed by profuse perspiration. The pulse becomes slow and irregular, the respirations slow and labored. Fibrillary contractions of the muscles and convulsions are generally observed, and after some time collapse sets in and is followed by unconsciousness and eventually by respiratory failure.

Action.—When veratrine is applied in ointment to the **Skin** the same prickling, warm sensation may be elicited locally, and some of the poison is absorbed, as is shown by these symptoms sometimes occurring in other parts of the body. The cause of this is, as in the case of aconite, stimulation of the terminations of the sensory nerves. This action causes violent sneezing and coughing when small quantities of veratrine come in contact with the sensitive mucous membranes of the nose and throat, and Sabadilla is therefore known popularly in Germany as Nieswurz (Sneeze-wort). After the irritant action has lasted for some time, the sensory terminations in the skin become less sensitive, and a feeling of numbness and of cold is noted. Protoveratrine seems to cause less irritation of the sensory terminations than veratrine, and the subsequent local anæsthesia is more complete.

The **Terminations of the Motor Nerves** are paralyzed in the frog by large quantities of veratrine, but this paralysis is not preceded by an increase in their irritability, as was formerly supposed.

Nausea and **Vomiting** which are invariably present in veratrine poisoning may be due in part to the irritation of the sensory terminations of the stomach, but must probably be attributed for the chief part to central action. The salivation may be merely secondary to this emetic effect, or the poison may act on the salivary gland directly. Nothing is known with certainty regarding the cause of the **Purgation**, but it is presumably induced by some action on the nervous mechanism of the intestine. The profuse **Perspiration** which follows the injection of large quantities of veratrine, and the cutaneous secretion noted in the frog, have been attributed to stimulation of the terminations of the nerves regulating the activity of the glands.

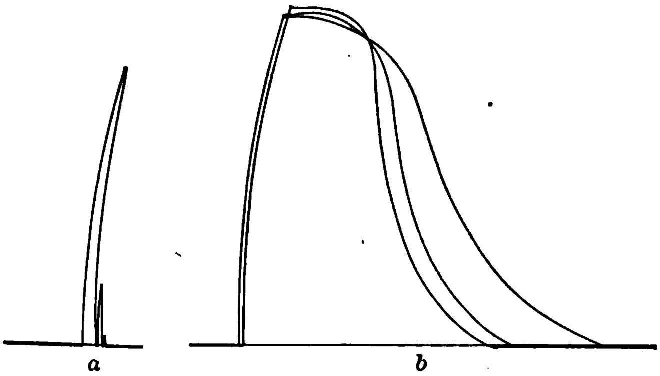
The most characteristic action of veratrine, however, is that on the **Striated Muscles**. If a small quantity be injected into the lymph-sac of a frog a curious clumsiness and awkwardness in the movements becomes apparent, and after a few minutes it is evident that this is due to inability to relax its muscles. When a muscle is exposed, it is seen to contract as rapidly as usual, but instead of immediately relaxing again, it remains shortened and offers resistance to the contraction of the opposing muscles. The animal can no longer coördinate its movements therefore; for example, it can no longer extend a limb immediately after flexing it, as it does ordinarily in crawling, and locomotion becomes very slow and ungainly.

This characteristic action is most easily seen on comparing the tracings obtained from a muscle stimulated directly by single induction shocks before and after the application of veratrine (Fig. 53). In the first part of the tracing it will be observed that the height of the contraction is increased by veratrine, but this feature sinks into

Less evidence of fatigue if veratrine injected after fatigue

the background before the marked prolongation of the second part of the curve. Instead of the almost instantaneous return to the base line seen in the normal tracing, the curve shows generally a slight undulation, and then a very slow fall, the period of relaxation generally being 20–30 times as long as that in the unpoisoned muscle, and the whole contraction lasting 5–10 seconds in favorable circumstances. If, however, the muscle be stimulated repeatedly at short intervals, so as to induce fatigue, the length of the curve decreases until it cannot be distinguished from the ordinary muscle tracing; a similar effect is produced by subjecting it to cold, or by heating it beyond a certain point, while moderate heat increases the abnormalities of the tracing. If an unpoisoned muscle be stimulated repeatedly, so as to induce fatigue, and veratrine be then injected, it is found that a marked improvement in the contraction occurs, so that while fatigue lessens the prolongation of the veratrine curve, veratrine removes to some extent the effect of fatigue. In the prolonged contraction more energy is used up than usual, and the amount of heat formed during muscular contraction is therefore increased by veratrine. Besides the alterations seen in the tracing, veratrine increases the irritability and absolute strength, so that the muscle reacts to weaker stimuli and contracts against a greater weight than usual.

FIG. 53.



Tracings of muscular contractions from the gastrocnemius of the frog. *a*, normal. *b*, three successive contractions taken at intervals of one minute, five minutes after the injection of veratrine. The contraction is higher and much more prolonged than in *a*, and the lever returns very slowly to the base line.

The muscular phenomena are best observed in the frog, but can also be elicited in warm-blooded animals, although in the latter they do not play such an important rôle in the symptoms of poisoning. In the frog the muscle is finally paralyzed, but this does not occur in mammals, as here the respiratory centre fails long before the quantity of veratrine necessary to induce this effect has been absorbed.

The first explanation that suggests itself for the curious muscular phenomena, that they are due to some change in the nervous system, is negatived by the fact that excised muscles show exactly the same reaction. Bezold explained the prolongation by supposing that a change was produced in the muscle substance, by virtue of which a single stimulus was enabled to set up a tetanic contraction; but this is shown to be incorrect, for if the nerve of another nerve-muscle preparation be laid on the veratrinized muscle, no secondary tetanus is set up in it, as would be the case if the first muscle were undergoing tetanic contraction. The generally accepted view is that veratrine increases the catabolic changes in muscle, and thereby induces a prolongation of the period of active contraction, as well as an increase in the height of contraction and in the absolute strength. Fatigue, by reducing the amount of substance capable of undergoing catabolic change, and cold, by increasing its stability, counteract the effects of veratrine.

In the tracing of veratrinized muscle a curious undulation is frequently seen at the top of the contraction, or the ascent may at first be rapid, then slower, and then again more rapid. This has been ascribed to veratrine acting differently on the two forms of muscle fibre, the gray and the red, but this explanation has recently been shown to be erroneous (Carvallo and Weiss). Botazzi supposes that the initial contraction is due to the anisotropous substance, while the secondary slower and prolonged contraction is induced by increased activity of the sarcoplasm. The electrical organ of the torpedo is apparently affected by veratrine in the same way as striated muscle.

Waller has recently shown that veratrine abolishes the irritability of the peripheral nerves when a solution is applied to them directly.

Protoveratrine differs entirely from veratrine in its effects on the muscles and the terminations of the motor nerves. The latter are not paralyzed even by the largest quantities, while the contraction of the muscle is rather shortened than prolonged. The contraction is higher and the absolute strength is increased, but fatigue is induced more readily than in the unpoisoned muscle, so that protoveratrine appears to increase the muscular force temporarily, but leads to its early exhaustion.

Circulation.—The ventricular muscle of the frog's heart is affected by veratrine in very much the same way as the ordinary striated muscle, while the auricular muscle, consisting chiefly of unstriated fibres, is much less altered. The ventricular systole is at first stronger and more prolonged; somewhat later one part of the ventricle is seen to remain contracted during the alternate diastoles of the rest, and waves of contraction spread over the heart resembling the peristaltic movements of the intestine rather than the ordinary contractions of the heart. The whole ventricle is smaller than usual, and but little blood is expelled into the aorta. Still later the persistent contraction spreads over the whole ventricle, so that it dilates only half as often as it did at first, while the auricles maintain their original rhythm. This is evidently due to action on the muscle; the contraction is so prolonged as to limit the number of diastoles, and the ventricle can

Prolonged ventricular contraction. First peristaltic waves.
Frogs In man, I stimulation, little direct stimulation.
Death from resp. paralysis. Stim.) Cord + medulla = Convulsions

therefore react only to every alternate contraction of the auricle. After this "half-rhythm" has persisted for some time, the contractions become slower and weaker, and the heart finally comes to a standstill. The behavior of a frog's heart under veratrine resembles closely that characteristic of the digitalis series.

In mammals the chief circulatory symptoms arise from stimulation of the medullary centres resembling that seen in the earlier stages of aconite poisoning. The stimulation of the cardiac inhibitory centre produces slowing of the heart and a decrease in its output, while at the same time the peripheral vessels are contracted by the increased activity of the vasomotor centre. After large quantities the terminations of the vagus are paralyzed, and the vasomotor centre is at the same time depressed, so that the pulse becomes quicker, but the blood-pressure is somewhat lowered. In the mammalian heart no such prolongation in the systole is seen as in the frog's, but that a slight stimulant action is exercised by veratrine is shown by the fact that very large doses quicken the rhythm even after atropine. Veratrine, therefore, seems to resemble aconitine in its effects on the mammalian circulation, but much larger quantities are required to produce the same effects, and the more evident symptoms of stimulation of the myocardium are not elicited.

The **Respiratory Changes** under veratrine also resemble those under aconitine, and in both the cause of death is the same—paralysis of the respiration.

The **Central Nervous System** seems to undergo stimulation under veratrine as under aconitine. This is evidenced by the convulsions seen in mammals as well as by the stimulation of the medullary centres already noted. After large quantities of the poison this stimulation gives place to paralysis, terminating in failure of the respiration. The highest centres seem less affected than the spinal cord and medulla oblongata, for complete consciousness has remained until immediately before death in several fatal cases.

The **Temperature** is sometimes found lower than the normal after veratrine, probably owing to the slowing of the circulation. In other cases, when the convulsive movements are very marked and the heat production is therefore much increased, the temperature has been found somewhat higher than usual. In cases of poisoning in mammals atropine is said by Lissauer to have some value, probably owing to its action on the respiratory centre and on the vagus terminations in the heart.

As regards the other alkaloids of this series, jervine, sabadilline and sabadinine seem to possess the same action as veratrine, but are much less poisonous. Protoveratrine, which, as has been said, differs from veratrine chiefly in not prolonging the muscular contraction and in the effects on the sensory terminations, is much more poisonous. Its action resembles that of aconitine as much as that of veratrine, and it may therefore be regarded as a link connecting the two groups.

Locally, safer than aconite for neuralgia. Hardly internally.

PREPARATIONS.

.0025 **Veratrina** (U. S. P., B. P.), a mixture of alkaloids obtained from the seeds of Asagræa officinalis (U. S. P.); a mixture of alkaloids prepared from cevadilla, the dried, ripe seeds of Schœnocaulon officinale (B. P.), forms a white or gray, amorphous or semi-crystalline powder without odor, but causing intense irritation of the nostrils, with an acrid taste and leaving a sensation of tingling and numbness on the tongue. It is insoluble in water but soluble in alcohol. It contains veratrine and the other alkaloids of the plant. ✓Dose, 2 mg. ($\frac{2}{30}$ gr.).

Unguentum Veratrinæ (U. S. P., B. P.), 4 per cent.

Oleatum Veratrinæ (U. S. P.), 2 per cent.

Veratrum (U. S. P.), the rhizome and roots of Veratrum viride, American or Green Hellebore, or of Veratrum album, White Hellebore.

Fluidextractum Veratri, 0.1 c.c. (1½ mins.).

Tinctura Veratri, 1 c.c. (15 mins.).

Therapeutic Uses.—The therapeutic uses of the members of this series are extremely limited. Veratrine is used in the form of the oleate or ointment as an external application in cases of neuralgia and is certainly a safer remedy than aconite. Neither its pharmacological action nor therapeutic experience supplies any indications for its internal use. Veratrum is used internally in the same class of cases as aconite, but might well be discarded from the pharmacopœia.

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XXIII. EMETINE (IPECACUANHA).

Ipecacuanha (Cephælis Ipecacuanha) has long been used for its emetic and expectorant virtues, and was until recently believed to contain only one alkaloid, *Emetine.* Paul and Cownley have shown, however, that this so-called principle is really made up of three distinct alkaloids, *Cephœline* ($C_{14}H_{19}NO_2$), *Emetine* ($C_{14}H_{18}(CH_3)NO_2$), and *Psychotrine,* the first two of which are quinoline derivatives and produce almost identical effects, while psychotrine is nearly inert. Their chief action is exerted on the alimentary canal, although they are also local irritants.

Symptoms and Action.—When administered internally emetine has a bitter, acrid taste, and produces a copious salivary secretion, followed later by nausea and vomiting with the usual attendant symptoms. The drug is generally largely eliminated by vomiting, so that no further effects are observed.

Ipecacuanha's chief alkaloid is emetine. Local irritant, esp. for
with nausea & expectoration + cough. Absorption & vomiting eliminates
the drug. Hypo causes collapse. Marked fr. local idiosyncrasy—tears
& sneezing. Emesis is peripheral irritation, not on centre
death from cardiac failure.

When injected hypodermically, however, it induces nausea, vomiting and purging, and blood is frequently voided in the stools, a condition of collapse follows, and the animal generally dies of exhaustion in the course of a few hours after the onset of the symptoms. Very large quantities injected subcutaneously or intravenously may fail to elicit vomiting, but the collapse symptoms appear, and after some weak convulsive movements, the animal dies of cardiac failure. In those cases in which death follows rapidly on the injection, no pathological lesions may be found after death, but in experiments where smaller quantities are injected, and the animal survives for 18–24 hours, the stomach and intestine often exhibit the appearances of an acute gastro-enteritis. The mucous membrane is swollen, congested and often covered with a muco-purulent secretion or studded with ecchymoses, and in dogs ulceration is often present. A lesion which is not by any means constant, but which occurs in a considerable number of animals and especially in rabbits, is œdema of the lungs.

Emetine possesses a powerful **Irritant Local Action,** which is, however, much more marked in certain individuals than in others. The smallest quantity of the powdered root of ipecacuanha is sufficient to induce in the subjects of this idiosyncrasy considerable swelling and injection of the conjunctival and nasal mucous membranes, with salivation, tears, sneezing, coughing and bronchial catarrh. When applied to the skin as a liniment, it produces redness, itching and occasionally a pustular eruption, but Lowin states that the alkaloids are devoid of action on the subcutaneous tissues. Its action on the alimentary canal also indicates its irritant properties. It has been much discussed whether the emesis is wholly due to this irritant action on the gastric mucous membrane, or whether emetine, like apomorphine, has a specific action on the centres in the medulla oblongata controlling vomiting. In view of the fact that emetine, like many other irritants when injected subcutaneously, has a specific action on the alimentary canal it seems unnecessary to have recourse to any action on the central nervous system, and almost all the facts brought forward as evidence of this supposed central action have been disproved.

It is sometimes stated that section of the vagus nerves does not prevent ipecacuanha from causing vomiting, whereas if it only irritated the stomach, the division of these nerves (which are probably the chief sensory nerves of the stomach) ought to prevent it by hindering the impulses reaching the medulla and setting up reflex processes there. But this statement has been contradicted, and no great weight can be laid on the argument in any case, because section of the vagus alone causes violent and persistent vomiting very often. Thumas states that the application of emetine solutions to the medulla provokes vomiting, but this method is so open to objection that his inference that the alkaloid acts on the vomiting centre can hardly be regarded as justifiable. On the other hand, it may be urged that if emetine acted on the medullary centre, vomiting ought to follow after smaller doses and more quickly when it is injected subcutaneously, being thus more rapidly absorbed, than when it is taken up from the stomach. But this is not the case, for ipecacuanha causes emesis as soon and in as small quantities when it is administered by the stomach, whereas apomorphine, which acts on the centre directly, acts much more rapidly and efficiently when it is injected subcutaneously. While the question cannot be said to be definitely settled, almost all the facts point to peripheral gastric, and not to central action.

Nausea + vomiting = usual sym. of weakness, + secretions.
Crude drug used as has much ta. + less chance of purging.

Emetine injected into a vein weakens the heart's action, and induces a fall of blood-pressure, but when it is injected subcutaneously or given by the mouth the heart is much less affected.

In the frog emetine does not cause vomiting, but a slowly advancing central paralysis follows its injection, the spontaneous movements ceasing early, and later the reflex excitability disappearing. The contractions of the heart are rendered weak and irregular, and eventually cease from paralysis of the cardiac muscle.

The nausea and vomiting are accompanied by the usual symptoms—muscular weakness and depression, increased secretion of saliva and of mucus by the glands of the throat and respiratory passages, often perspiration and generally temporary acceleration of the pulse. (See apomorphine, page 240.) Most of the researches on which the above statements are based have been performed with a mixture of the alkaloids, but the two chief of these resemble each other very closely in their effects, cephæline being somewhat more powerful than pure emetine.

Emetine and cephæline have not been used in practical therapeutics, various preparations of the crude drug being prescribed instead. Their isolation is so difficult that it seems unlikely that the pure alkaloids will be made use of in the near future, and from a comparison of their effects with that of ipecacuanha it scarcely seems desirable that they should be introduced. For ipecacuanha is much less liable to produce purging than emetine, probably because the solution of the alkaloids is retarded by the presence of large quantities of tannin bodies and other impurities, while at the same time the emetic action is but little slower than that of emetine.

PREPARATIONS.

2-4 g in dysentery
emetic 1 g
expect. .06
1 cc expect
emetic

U. S. P.—**Ipecacuanha**, the root of Cephælis Ipecacuanha or of C. acuminata, contains at least 2 per cent. of alkaloids. The powdered root is prescribed in dysentery in quantities of 2–4 G. (30–60 grs.); emetic, 1 G. (15 grs.); expectorant, 0.06 G. (1 gr.).

Fluidextractum Ipecacuanhæ, expectorant, 0.05 c.c. (1 min.); emetic, 1 c.c. (15 mins.).

SYRUPUS IPECACUANHÆ, } expectorant, 1 c.c. (15 mins.); emetic, 15 c.c.
VINUM IPECACUANHÆ, } (4 fl. drs.).

.5 cc TINCTURA IPECACUANHÆ ET OPII contains 10 per cent. opium, *i. e.*, is of the same strength as laudanum, 0.5 c.c. (8 mins.).

.5 g PULVIS IPECACUANHÆ ET OPII (10 per cent. each of ipecacuanha and opium), Dover's Powder, 0.5 G. (8 grs.).

B. P.—**Ipecacuanhæ Radix**, the dried root of Psychotria Ipecacuanha, expectorant, ¼–2 grs.; emetic, 15–30 grs.; in dysentery, 30–60 grs.

Extractum Ipecacuanhæ Liquidum, expectorant, ¼–2 mins.; emetic, 15–20 mins.

VINUM IPECACUANHÆ, expectorant, 10–30 mins.; emetic, 4–6 fl. drs.

Trochiscus Ipecacuanhæ, contains ¼ gr. of the powdered root.

TROCHISCUS MORPHINÆ ET IPECACUANHÆ, each contains $\frac{1}{36}$ gr. of morphine hydrochloride.

PULVIS IPECACUANHÆ COMPOSITUS, Dover's Powder, 10 per cent. each of ipecacuanha and opium, 5–15 grs.

Pilula Ipecacuanhæ cum Scilla, 4–8 grs. This pill is formed from Dover's Powder, and contains about 5 per cent. of opium.

In emesis for children where hypo of apomorphine contraindicated as expectorant in infl. of resp. tract. Acts longer than apomorph & less depressant than tart. emetic. Dovers to allay cough - Dovers as diaphoretic in chills & commencing catarrh of resp.) Specific in amoebic dysentery - 30-60 gr + laudanum to prevent vomit then less down to 10 gr

Therapeutic Uses.—Ipecacuanha has been largely employed as an emetic, and although it has been replaced for some purposes, notably in cases of poisoning, by apomorphine, it still has a certain field of usefulness in cases in which an emetic is indicated, but in which the hypodermic method is objectionable, as in children. At present ipecacuanha is used chiefly as an expectorant in the treatment of inflammatory conditions of the respiratory passages. For this purpose it is prescribed in very much smaller quantities than those necessary to produce emesis. It acts indirectly through its nauseating properties, and has the advantage that its action is much more prolonged than that of apomorphine, and at the same time is not so depressant as that of several metallic substances, such as tartar emetic, which are used for the same purpose. It increases the secretion of the bronchial mucous membrane, and further tends to render it more fluid, so that the mucus can be coughed up more easily. The increased secretion may also be of service by protecting the inflamed and irritable membrane from the cold air and thereby lessening the cough; opium is often added in order to further allay coughing by depressing the centre, the well-known Dover's powder being a favorite prescription for this purpose. When the secretion of the bronchi is already excessive, and the cough is rather to be encouraged than repressed, these preparations are of course contraindicated.

Ipecacuanha is also employed as a diaphoretic, either alone or more commonly as Dover's powder. The perspiration is not so copious as that following pilocarpine and other diaphoretics, but resembles rather that produced by warmth applied to the skin. Dover's powder is therefore a common remedy in chills and in commencing catarrh of the respiratory passages.

Ipecacuanha is used very largely in dysentery, particularly in amœbic dysentery, in which it seems to act almost as a specific. Its effect is attributed by some authorities to the large amount of tannin contained in the root, and a preparation of ipecacuanha from which the alkaloids have been removed (*Ipecacuanha Deemetinisata*) is said to be as valuable in these cases as the unaltered drug. Others are inclined to ascribe some of the virtues of ipecacuanha to the alkaloids, and deny that the same results are obtained by the use of this preparation. The purified powder has the advantage of not causing any nausea or vomiting, and is certainly to be preferred to the crude root if the claims of its advocates prove to be well founded. Very large quantities of the powdered root are generally required in dysentery. Many prescribe enough to cause vomiting at first, and then follow this up with smaller quantities which are used along with morphine or ice, or with sinapisms to lessen the nausea and vomiting. Others give a few drops of laudanum at once, and when the medullary irritability is thus reduced, and there is less danger of vomiting, prescribe 30–60 grs. (2–4 G.) of the powdered root, and continue the treatment with smaller doses.

Ipecacuanha has been recommended in very small quantities as a stomachic, even in cases of vomiting, and its action on the mucous membrane might be expected to be of value in some cases; but it very often fails to have any effect, and is not widely used for this purpose.

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XXIV. COLCHICINE.

Colchicine and *colchiceine* are two nearly related bodies found in the seeds and corm of Colchicum autumnale, which owes its activity to their presence. They are generally included among the alkaloids, but differ from the other members of this class in possessing an acid reaction. Their chemical structure is still imperfectly known, but they do not seem to contain a pyridine ring; colchicine $[C_{15}H_9(OCH_3)_3(NHCOCH_3)COOCH_3]$ is the methyl ester of colchiceine $[C_{15}H_9(OCH_3)_3(NHCOCH_3)COOH]$. These two principles are apparently identical in their effects, which are observed chiefly in the alimentary canal.

Symptoms.—No symptoms whatever follow the use of colchicum in ordinary therapeutic quantities. After the administration of a poisonous dose to man or animals several hours elapse before any symptoms are elicited, and the amount injected has but little influence on the duration of this preliminary stage. Whether given by mouth or hypodermically, colchicine produces symptoms of discomfort in the stomach and intestine. Pain in the gastric region is followed by salivation, nausea, vomiting and diarrhœa. At first the evacuations are the ordinary contents of the stomach and intestine, but afterwards a quantity of sticky mucous fluid may be ejected, often streaked with blood. Later, a condition of depression, apathy and collapse follows, and the movements become slow and difficult, more especially in the posterior extremities, which eventually become completely motionless; the paralysis then progresses upwards until the movements of the fore limbs and respiratory muscles are involved, when death occurs from asphyxia. In man the intelligence remains until death, though there is generally some giddiness and precordial anxiety and occasionally some confusion or even delirium preceding the collapse.

In mammals poisoned with colchicine the alimentary canal exhibits all the appearances of acute gastro-enteritis, with numerous ecchymoses, especially in the upper part of the bowel. In less acute cases these inflammatory symptoms are less marked, and in man there is seldom more than catarrh of the duodenum.

The **Circulation** is but little affected apparently. In animals the blood-pressure and heart rhythm remain normal, and though a small, rapid pulse may be one of the features of the poisoning in man, this is due to the collapse rather than to any direct action on the circulatory organs.

The **Respiration** is slow, but is deep and full at first. Later it becomes shallow, and the failure of the centre is the cause of death, the heart continuing to beat for some time afterwards.

The **Movements of the Bowel** are much hastened when the symptoms set in, and Dixon states that colchicine acts on the bowel in the same way as pilocarpine, and that its action is antagonized by atropine; but this is entirely inadequate to explain the acute inflammatory appearances, which are evidently due to an irritant action on the mucous membrane. Increased movement is said to be induced in the plain muscle of the spleen, uterus and bronchial muscle from a pilocarpine-like action.

When **Locally Applied** to sensitive mucous membranes, or when injected hypodermically, colchicine is intensely irritating, producing redness and prickling in the skin, and a burning sensation in the mouth and throat.

The **Nervous Symptoms** are supposed by some to be due to a direct action on the central nervous system, but are to be ascribed rather to a condition of collapse produced indirectly through the action on the abdominal organs.

The influence of colchicine on the **Kidneys** varies, for in some cases complete anuria is produced for many hours, while in others the urine is slightly increased. The constituents of the urine are not materially altered by ordinary therapeutic doses of colchicum, and, in particular, the uric acid shows no constant change in amount. In animals bloody urine is sometimes passed after colchicine.

In poisoning with colchicine the leucocytes are at first reduced in the peripheral circulation, but afterwards increase to beyond the normal number.

All of these symptoms are exactly those caused by a large number of poisons, including some of the bacterial toxins and the heavy metals. Many local irritants when injected into the blood or when absorbed from the subcutaneous tissue or the alimentary canal, exercise an immediate, local action, which betrays itself in pain, or ecchymosis and swelling at the point of injection, but these symptoms pass off in a short time and the animal becomes apparently normal for many hours or even days. At the end of this time, however, symptoms begin to develop at two points—in the alimentary canal and in the kidneys. The reason probably is that the poisons are excreted at these points and are either freed from some harmless combination in which they have circulated in the tissues, or perhaps collect in larger quantities in the excretory organs. At any rate, irritation and later acute inflammation are set up at these points. At first the irritation excites only diarrhœa and diuresis, but as it goes on, gastro-enteritis and anuria or hæmaturia may be produced.

The symptoms from the intestine and kidney may not be equally well marked; at one time the one becomes inflamed while the other is only subjected to mild stimulation, while at other times both are the seat of acute inflammation. The inflammation of the bowel produces a condition of collapse, which is seen also in various intestinal diseases, such as cholera. Sometimes the poisons (and also cholera) produce no very marked symptoms of gastro-intestinal disorder, but rather those of collapse, but there is no reason to believe that the collapse is due to any direct action on the central nervous system.

In the frog colchicine has little or no effect, but if the solution be exposed for some time to the air, it causes a prolongation of the muscular contraction similar to that seen after veratrine, and eventually a tetanus resembling that due to strychnine. Jacobj therefore believes that in mammals the effects are not produced by colchicine itself, but by a substance formed by its oxidation in the tissues, oxydicolchicine. The frog's tissues are unable to oxidize colchicine, but if oxydicolchicine be formed by the exposure of colchicine to the air, it produces these symptoms. Oxydicolchicine causes the same symptoms in mammals as colchicine.

Preparations.

Colchici Cormus (U. S. P., B. P.), the corm or bulb of Colchicum autumnale, containing 0.35 per cent. of colchicine, 0.1–0.3 G. (2–5 grs.).

Extractum Colchici Cormi (U. S. P.), 0.065 G. (1 gr.).

Extractum Colchici (B. P.), ¼–1 gr.

VINUM COLCHICI (B. P.) (10–30 mins.).

Colchici Semen (U. S. P.), **Colchici Semina** (B. P.), the seed of Colchicum autumnale, containing 0.55 per cent. of colchicine, 0.2 G. (3 grs.).

Fluidextractum Colchici Seminis (U. S. P.), 0.2 c.c. (3 mins.).

Tinctura Colchici Seminis (U. S. P.), 2 c.c. (30 mins.).

Tinctura Colchici Seminum (B. P.), 0.3–1 c.c. (5–15 mins.).

Vinum Colchici Seminis (U. S. P.), 2 c.c. (30 mins.).

Colchicina (U. S. P.) ($C_{22}H_{25}NO_6$), an alkaloid obtained from colchicum, pale yellow in color, with a bitter taste and characteristic odor; soluble in 22 parts of water and in alcohol. Dose, 0.5 mg. ($\frac{1}{120}$ gr.).

Therapeutic Uses.—Colchicum has long been used in gout on purely empirical grounds. In fact, the pathology of gout is so obscure that no rational treatment for it can be looked for at the present day, and the efficacy of colchicum in this disease can, therefore, be argued solely from clinical experience. Most physicians state that the pain in gout is rapidly relieved by colchicum wine and that the attacks may be shortened by its judicious use. Others are less confident of its beneficial action, but the evidence is strong enough in its favor to justify its use in most cases, especially as therapeutic doses do not seem to involve any deleterious symptoms. Some attempt has been made to place the practice on a rational basis by showing that it increases the excretion of uric acid. But this increase in the uric acid excretion is by no means a constant result of colchicum medication, for it not infrequently has the opposite effect, and in gout the uric acid excretion does not seem to be modified at all by colchicum. It is now generally agreed that gout is not due to a simple failure of the excretion of uric acid, so that these results do not serve either to support or condemn the treatment by colchicum. Several investigators state that the excretion of endogenous uric acid undergoes some augmentation under colchicum, and this may perhaps throw some light on the subject in the future, though it is not clear whether this indicates an increased formation of the uric acid or its diminished destruction in the tissues.

Colchicum has also been used in chronic rheumatism, but here it is of little or no benefit.

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XXV. SAPONIN, SAPOTOXIN AND SOLANINE.

Under this group are arranged a number of glucosides which have many features in common both in their chemical properties and in their pharmacological action. Many of them have not yet been completely isolated, and it seems not unlikely that several which are now believed to be distinct, will prove to be identical. Kobert has found that many of them may be arranged in a chemical series $C_nH_{2n-8}O_{10}$. Some have an acid reaction and form salts with the alkalies, while all possess the characteristic glucosidal reaction, being decomposed by acids and ferments into sugars and unknown inactive substances. The most poisonous among them are designated by the general term of *Sapotoxins,* while *Saponin* may be used to include the less active ones and certain innocuous isomers of the sapotoxins which are formed from them by boiling with alkalies. These terms as well as the popular names of several of the plants from which the active principles are derived, refer to the property they possess of forming frothy, soap-like solutions in water and of holding insoluble bodies in suspension in it. Very often several of these bodies are found in a single plant, either several powerfully poisonous ones (sapotoxins), a mixture of sapotoxins and saponins, or saponins only.

Saponins or sapotoxins are found in about 150 species of plants. The chief of these are:

Quillaja saponaria, or soapbark (containing *quillaja-sapotoxin* and *quillajac acid*).

Saponaria officinalis, or soapwort (*saporubrin* and *saponin*).

Cyclamen Europeum, or sowbread (*cyclamin*).

Polygala senega (*senegin* and *polygalic acid*).

Agrostemma githago, or corncockle (*agrostemma-sapotoxin* and *acid*).

Gypsophila struthium and other species (*gypsophila-sapotoxin*).

Chamælirium luteum, or blazing star (*chamælirium-sapotoxin*).

Smilax, various species, including those known as sarsaparilla (*sarsaponin, sarsaparilla-saponin* and *parillin* or *smilacin*).

In addition to the plants, which owe their action to the presence of these bodies, a number of drugs contain saponins along with other more important principles. Thus an almost inactive saponin (*digitonin*) is met with in digitalis, and similar saponins probably occur in several others of the digitalis series, although they have not yet been isolated.

The most poisonous of these are the sapotoxins of quillaja, agrostemma and gypsophila, quillajac acid and cyclamin. Senegin is only about one tenth as poisonous as quillaja-sapotoxin, and the saponins prepared from the sapotoxins are still less dangerous.

Another body closely resembling the saponins in action is *Solanine,* a glucosidal alkaloid found in many species of Solanum, such as S. nigrum (black nightshade), S. dulcamara (bittersweet), S. tuberosum (potato), and probably in some species of Scopola. In Solanum nigrum and S. dulcamara it is accompanied by small quantities of one or more bases resembling atropine, while in dulcamara a glucosidal body, *Dulcamarin,* has been found also belonging to the sapotoxin series. Solanine breaks up on being heated with acids into sugar and a base, *Solanidine,* which retains the poisonous action. In some plants both solanine and solanidine seem to be present.

Its chief importance arises from its occurrence in the potato, which has given rise to widespread poisoning in several instances. The amount of solanine in the potato is in general too small to provoke poisonous symptoms, even when enormous quantities are eaten, but when the potatoes begin to sprout in damp cellars, the percentage of solanine rapidly increases, especially in the green buds and the small young tubers. In old, rotting potatoes it may also become dangerously high, but cases of poisoning are more likely to arise from the use of the green, unripe potatoes than from those which are obviously unfit for use. Weil states that the increase in solanine seen in potatoes that have been kept too long is due to the presence of bacteria which form this alkaloid from the potato.

In any case the potato skins contain nearly half of the solanine, and if these be removed before boiling, a considerable part of the alkaloid contained in the edible part is extracted by the water.

Action.—The sapotoxins possess a very irritant local action, and produce acute inflammation of the alimentary canal and extravasations in various organs, when they are carried to them by the blood. They also destroy the red blood cells when brought into contact with them.

They have a harsh, acrid, unpleasant taste, and when swallowed provoke nausea and often vomiting, with pain and colic, and less frequently diarrhœa. They are not absorbed by the normal epithelium of the alimentary canal, and seem to undergo decomposition in the bowel, and therefore fail to produce general symptoms. Thus pigs feed with avidity on Cyclamen and are unharmed by it unless some lesion of the intestine is present. The unbroken skin is not affected by a single application as a general rule, and absorption is extremely slow from the subcutaneous tissues, in which they act as irritants, however, and produce inflammation and suppuration. The sapotoxin derived from Agrostemma differs from the others in being absorbed fairly rapidly from the alimentary canal and from the subcutaneous tissues, so that more dangerous symptoms may arise from it than from the other members of the series.

In an epidemic of solanine poisoning from potatoes described by Schmiedeberg, the symptoms consisted of headache, colic, vomiting and diarrhœa, general depression and weakness, and some mental confusion. In severe cases pallor or cyanosis, dilated pupils, short periods of unconsciousness with acceleration and then slowing of the pulse were observed. All the patients recovered in the course of ten days. In many cases some rise of temperature was noted. When solanine is administered by the mouth, most of it is decomposed, for very little reappears in the stools and urine as solanine and solanidine.

When these bodies are injected directly into the blood vessels, they induce much more characteristic changes, which very often prove fatal after a longer or shorter interval. Very large quantities thus injected may kill animals within a few minutes from respiratory paralysis, and no characteristic appearances are to be found post-mortem. Smaller doses induce depression, loss of appetite, sometimes vomiting and diarrhœa, general weakness and collapse, with some dyspnœa and irregular, feeble pulse. Weak convulsions appear just before the failure of the respiration, while the heart continues to contract for some minutes longer. In these cases ecchymoses are found in the serous membranes, pericardium, pleura and peritoneum, and occasionally in the kidneys. Endocarditis has been observed in some instances, but the most important alterations occur in the stomach and intestines, the mucous membrane of which is swollen and congested and contains numerous blood extravasations. The lymphatic glands of the abdominal cavity are also swollen and congested and often filled with hæmorrhages. Occasionally the kidneys are found to contain numerous blood casts, filling the lumen of the tubules, and in these cases albumin and hæmoglobin appear in the urine before death; these are more often elicited by solanine than by the sapotoxins. In Cyclamen poisoning (from intravenous injection) hæmoglobinuria is one of the earliest symptoms.

The saponin bodies are general protoplasmic poisons, destroying life whenever they come in contact with living tissues in sufficient concentration. Their irritant action on the mouth, throat and stomach is the cause of the nausea and vomiting observed when they are administered in this way, and they cause sneezing and coughing from the same action in the nose and throat. On other mucous membranes, such as the conjunctiva, and in wounds, they cause similar irritation and inflammation, which may be followed by suppuration. A form of local anæsthesia often follows this irritation, the termination of the sensory nerves apparently being benumbed, but the preliminary irritation precludes their use for this purpose.

Even the unbroken skin may be irritated when they are applied repeatedly or rubbed on in the form of ointment. This irritation is betrayed by redness, heat, itching and eventually by the formation of pustules. Their local effects when injected subcutaneously also indicate their irritant properties.

When the individual organs are exposed to the action of saponin bodies by the direct application of solutions to them, a similar poisonous action is elicited. Muscle contracts more weakly even in dilute solutions, is eventually entirely paralyzed, and is altered in structure, the transverse striæ of voluntary muscle and of the heart becoming very indistinct. Nerves exposed to solutions are also paralyzed in the same way, and the movements of cilia cease at once when they are exposed to sapotoxin bodies. The blood undergoes characteristic changes when it is acted on by saponin either in the vessels or in the test-tube. The red blood cells undergo rapid destruction and the hæmoglobin is freed in the plasma. Even one part of cyclamin added to 100,000 parts of diluted blood completely lakes the red blood cells, while hæmoglobin appears in the serum when considerably less poison is added. The other saponin bodies act less powerfully in this direction than cyclamin, but still produce distinct solution of the substance of the red corpuscles. When a saponin is injected into the blood of a living animal this destruction of the red blood-cells takes place to some extent, and the plasma contains hæmoglobin, while the blood corpuscles are considerably diminished in number. This hæmolytic action is not the result of changes in the hæmoglobin, but is due to the dissolution of the stroma of the corpuscles, which releases the hæmoglobin. The saponins have a strong solvent action on the lecithin of the stroma and its removal leads to the disintegration of the cell. This solvent action occurs more readily when the blood cells are suspended in normal salt solution than in the plasma or serum, and this has been shown to be due to the presence of cholesterin, which antagonizes the action on lecithin. Even when the hæmoglobin in the corpuscles is coagulated and saponin fails to induce laking, the structure of the corpuscle is altered, as is shown by its reaction to salts (Stewart).

The destructive effect of the saponins on other cells is probably the result of the solvent action on the lecithins which they contain.

The circulation in mammals is comparatively little affected until just before death, when the blood-pressure falls rapidly and the pulse becomes weak and slow. The heart continues to beat for a short time after the respiration ceases, but is very weak, and finally stops, even although artificial respiration is maintained. The isolated frog's heart is paralyzed by sapotoxins in the same way as the isolated muscle.

In many experiments death would seem to be caused by collapse following the changes in the alimentary canal. In others, however, when only small quantities of the poison have been injected, no such changes are observed, but the animal dies after a few days, presenting no distinct symptoms except general weakness and depression.

On the other hand, very large quantities injected into a vein may prove fatal within a few minutes, and here again no symptoms of intestinal action may appear. It is therefore believed that in addition to their irritant effects these bodies have a special action on the central nervous system, although it is impossible at present to specify its nature. The respiration is in all cases the first vital function to be suspended. Sapotoxin applied directly to the spinal cord in the frog first provokes convulsive twitching and clonic spasms and then paralyzes the animal, but it may be questioned whether it would have the same effect when carried in the blood.

The sapotoxins are poisonous to invertebrates apparently, unless they are protected by a shell, through which the poisons cannot penetrate. Thus the amœba and other simple organisms cease their movements, while intestinal worms are first excited and then paralyzed in the presence of some of the group.

Faust has recently shown that oleic acid has the same hæmolytic action as the saponin substances, and that some forms of anæmia are due to the red blood cells being destroyed by oleic acid absorbed in excess.

PREPARATIONS.

Quillaja (U. S. P.), **Quillaiæ Cortex** (B. P.), Panama bark, Soap bark, the inner bark of Quillaja saponaria.

Fluidextractum Quillajæ (U. S. P.), 0.2 c.c. (3 mins.).

Tinctura Quillajæ (U. S. P.), *Tinctura Quillaiæ* (B. P.), 2–4 c.c. (30–60 mins.).

Sarsaparilla (U. S. P.), the root of Smilax medica and other species of Smilax.

Fluidextractum Sarsaparillæ (U. S. P.), 2 c.c. (30 mins.).

Fluidextractum Sarsaparillæ Compositum contains sassafras, liquorice and mezereum. 2 c.c. (30 mins.).

Syrupus Sarsaparillæ Compositus (U. S. P.), contains liquorice, senna and the oils of sassafras, anise and wintergreen. 16 c.c. (4 fl. drs.).

Sarsæ Radix (B. P.), sarsaparilla, the dried root of Smilax ornata, imported from Costa Rica and known as Jamaica sarsaparilla.

Extractum Sarsæ Liquidum (B. P.), 2–4 fl. drs.

Senega (U. S. P.), **Senegæ Radix** (B. P.), the root of Polygala Senega.

Fluidextractum Senegæ (U. S. P.), 1 c.c. (15 mins.).

Syrupus Senegæ (U. S. P.), 4 c.c. (1 fl. dr.).

Tinctum Senegæ (B. P.), ½–1 fl. dr.

Infusum Senegæ (B. P.), ½–1 fl. oz.; as a draught, 2 fl. oz.

Therapeutic Uses.—The drugs of this group are all quite superfluous. They may be used to increase the bronchial secretion in cough through the nausea caused by their slight irritant action in the stomach, but they have no advantages over such drugs as ipecacuanha; the syrup of senega is often prescribed in expectorant mixtures for this purpose. Sarsaparilla has been supposed to have an obscure action on the nutrition, and has some reputation in the treatment of syphilis, but there is no reason to believe that it is of any service here or in any other condition, although it may be used as a vehicle for the administration of mercury and iodide of potassium. For this purpose the compound syrup U. S. P. or liquid extract B. P. is the best preparation. Quillaja has been used to some extent as an expectorant, more largely to form emulsions and to suspend insoluble powders. Its irritant action ought, however, to preclude its use for this purpose. It is frequently stated that members of the sapotoxin series are antidotes in digitalis poisoning; but this is founded on experiments in which both drugs were applied directly to the frog's heart, and there is no reason to suppose that they would oppose each other in man, especially if given by the mouth, as sapotoxin is absorbed only with great difficulty.

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XXVI. ASPIDOSPERMA, OR QUEBRACHO.

The bark of Quebracho blanco (Aspidosperma quebracho) contains a number of alkaloids which are probably very similar in chemical composition and which seem to possess almost the same action. They are *Aspidospermine, Aspidospermatine, Aspidosamine, Hypoquebrachine, Quebrachine* and *Quebrachamine.* Another species of Aspidosperma, Payta, contains two alkaloids, *Paytine* and *Paytanine,* of which Paytine resembles closely the Quebracho alkaloids in its pharmacological action.

These alkaloids all produce nausea, but even after large doses vomiting does not occur except after Aspidosamine. The nausea is accompanied by the usual concomitant symptoms—salivation, increased secretion of mucus in the respiratory tract, depression and alternately rapid and slow pulse. Large quantities often cause symptoms of central nervous stimulation, tonic contractions and convulsions. The respiration is quicker and deeper after small quantities, but after lethal doses becomes slow and weak, and finally ceases. Periodic respiration often occurs before the final standstill, a series of deep dyspnœic movements alternating with several shallow, insufficient ones. The failure of the respiration is the cause of death in mammals, the heart continuing to contract for some time longer. After Aspidosamine, there is no stage of quick and deep respirations, but the breathing is rendered slow at once and soon becomes periodic.

These symptoms are generally ascribed to a direct action on the central nervous system, which is first stimulated and then depressed. The chief seat of action seems to be the medullary centres and the spinal cord, although the basal ganglia may also be more or less involved. The stimulation of the medullary centres explains the nausea and vomiting and also the changes in the respiration, while the convulsions and increased reflex excitability point to the spinal cord.

The terminations of the motor nerves in voluntary muscles are paralyzed by aspidosamine and quebrachine in the frog, not by the other alkaloids; but all of them lessen the strength of muscular tissue and eventually paralyze it in these animals. Neither of these results has been observed to follow the injection of the alkaloids in mammals.

The circulation in mammals is affected indirectly through the nausea, and the heart may be slowed by very large doses. Wood states that even moderate quantities reduce the blood-pressure in the dog.

Eloy and Huchard observed diarrhœa and an increased secretion of urine occasionally follow the administration of the alkaloids, and they also describe a curious coloration of the blood which they ascribe to a diminution of the hæmoglobin. Penzoldt attributed the asphyxia to changes in the red cells, but the subject of the action of these alkaloids on the blood requires further investigation.

None of the quebracho alkaloids is very poisonous, but of the series quebrachine is the most toxic, and aspidosamine and aspidospermatine follow it closely. Aspidospermine, quebrachamine and hypoquebrachamine are comparatively weak.

Commercial "aspidospermine" is a mixture of all the alkaloids along with other bodies. It is sometimes prescribed in doses of 1–2 mgs. ($\frac{1}{60}$–$\frac{1}{30}$ gr.).

Aspidosperma was advised by Penzoldt in the treatment of dyspnœa from a variety of causes, and his statements have received a certain amount of support from clinicians. The special conditions in which it has been advised are dyspnœa from pulmonary disease, especially emphysema, and from cardiac weakness and asthma. Its action on the respiratory centre may explain to some extent the benefits derived from it, but the increased secretion of the bronchi produced by the nausea may also be of some importance.

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XXVII. QUININE.

The barks of various species of Cinchona and Remijia (Cuprea) contain numerous alkaloids which seem to resemble each other closely in their chemical and pharmacological properties. The best known of these are *Quinine, Quinidine* or *Conquinine, Cinchonine* and *Cinchonidine;* the others, amounting to some twenty in number, are believed to resemble these in their effects on the organism, but very little has been done to determine this, and nothing is known regarding their relative activity.

The cinchona alkaloids are derivatives of quinoline. Cinchonine and cinchonidine are isomeric ($C_{19}H_{22}N_2O$) and perhaps contain two quinoline molecules, while quinine and quinidine ($C_{20}H_{24}N_2O_2$) are methoxyl compounds of cinchonine.[1]

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[1] The other alkaloids of this series which have been identified are homocinchonidine, conquinamine, quinamine, cusconine, concusconine, aricine, cusconidine, cuscamine, cuscamidine, hydroquinine, hydroquinidine, hydrocinchonine, cinchonamine, quairamine, conquairamine, quairamidine and conquairamidine, while several

Ther. Eff. Cinchona barks contain many alkaloids resembling quinine in action; also tannins. A protoplasm poison. Exclude strychnine's action on nervous matter, it resembles quinine in its effects.

esp. destructive to malaria + putrefactive organisms. Excited then paralyzed

Cinchona bark contains besides these alkaloids several acids, including tannins, and some neutral substances.

The cinchonas are natives of Western South America, but are now cultivated in India and Java. It seems questionable whether the virtues of the bark were known by the native Indians before the invasion of the Spanish, and its introduction into medicine dates from about 1630–1640; its name bears testimony to its efficacy in the case of the Countess of Chinchon in 1638.

Action.—Quinine differs from most of the other important alkaloids in acting not on some specialized form of living matter, but on the general nutrition of almost all forms of protoplasm. Other alkaloids, such as strychnine, are also possessed of similar effects as regards nutrition, but their strong affinity for, and intense action on some special tissue, prevent their effects on the fundamental properties of living matter from being elicited in the higher animals. Quinine is therefore often termed a protoplasm poison because its action extends with but little variation throughout most forms of living matter; on the other hand, the marked effect of strychnine on the nerve cell causes it to be classed among nerve poisons, although in organisms devoid of a nervous system it resembles quinine in its effects. The effects of quinine on protoplasm generally consist in transitory augmentation of its activity, followed by depression and death.

The action of quinine on **Undifferentiated Protoplasm,** such as is found in the unicellular organisms and in the ovum, is therefore of greater interest than that of most alkaloids. Binz found that while very minute quantities sometimes increase the movements of the amœba and infusoria at first, large amounts paralyze them immediately, and the protoplasm assumes a darker granular appearance. The rhythmic movements of ciliated organisms are rendered slow and finally arrested by very dilute solutions, but no other organism is so susceptible to the action of quinine as that which induces malaria in man. The microbes of putrefaction are also acted upon by quinine, although they seem more resistant than the protozoa; still, quinine solutions have considerable antiseptic power, equalling that of carbolic acid, according to some observers. The alcoholic, lactic and butyric fermentations are retarded, or entirely prevented by quinine through its effects on the organisms, but it is apparently devoid of action on some of the lower forms, for moulds (Penicillium) grow freely in solutions of the salts; so that the alkaloid seems to have a selective action here, such as is observed also in its effects on the ferments of the higher animals. Another example of its action on the vegetable cell is that discovered by Darwin in some insectivorous plants (Drosera), in which the movements seem to be first excited and later paralyzed by the quinine salts.

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others are said to have been separated by some authorities, but are rejected by others. The acids generally acknowledged to be present in cinchona are quinic, quinovic, quinotannic, quinovatannic, caffeotannic and oxalic, while the neutral bitter substances have been named quinovin, quinova-red and cinchona-red.

Destruction to reproductive cells + leucocytes. No. diminished + in great quantities migration affected.

The influence of quinine on the reproductive cells of animals has been carefully studied by O. and R. Hertwig, who found that both the spermatozoön and the ovum of the sea-urchin are injured by the addition of quinine to the sea-water, the movements of the former being paralyzed, and the stages preceding impregnation in the latter progressing more slowly, or actually retroceding. When quinine is applied after the male nucleus has entered the ovum, the complete conjugation is delayed and the whole process is rendered abnormal by the admission of several spermatozoa. Quinine applied still later prevents or delays the division of the ovum through its effects both on the nucleus and on the general protoplasm of the cell.

The individual cells of more complex organisms are affected in the same way as these more simple ones. This was first demonstrated in the leucocytes by Binz, and after some opposition has been generally accepted. When a drop of blood is examined under the microscope the white cells are observed undergoing constant changes of form and position exactly similar to those of the amœba, but minute quantities of a quinine salt are sufficient to stop all movements at once, and the leucocytes assume a spherical form, become darker in color and granular, and soon break up into débris. In the blood vessels similar changes occur when quinine is applied locally, as to the frog's mesentery; the leucocytes again become darkly granular, and ceasing their creeping movements, are carried along by the current much more rapidly than usual. They are no longer observed to push their way through the vessel walls, and if they have already penetrated into the tissues their movements are arrested. If irritation be applied to the part, no such accumulation of leucocytes occurs in the tissues as in the unpoisoned animal, and if an irritant has been applied first and the leucocytes have poured out of the vessels before the quinine is applied, the process is arrested at once on its application. This effect was explained by Binz as due to the poison acting on the leucocytes, and although attempts have been made to explain it by some change produced on the vessel wall by the drug, there now seems no reason to question the correctness of his view. Similar results are observed when the drug is not applied locally, but carried to the part by the vessels; the movements of the leucocytes in the vessels are less distinct; they are carried along passively in the general current, assume a spherical form, and have much less tendency to escape into the general tissues, and at the same time the number of the leucocytes in the blood undergoes a considerable diminution. It would be unjustifiable to infer from these experiments that the therapeutic dose of quinine inhibits the movements of the white blood cells in the human body, and it is no part of Binz's theory that this occurs. The effect of quinine on the leucocytes is merely an example of its effects on the tissues generally. At the same time the number of leucocytes in the human blood is diminished by ordinary quantities of quinine, showing that the action on the frog's leucocytes extends also to those

Dec. oxygen power of blood lessened — action on [illegible]. Quinine hinders all living processes — movements, chemistry, ferments. Stim. 1st then depression & resp. > death. Circ. stim. then depressed. Vol. muscle — easily fatigues.

of man, even when the quinine is absorbed from the stomach and intestine.

Other evidence of the action of quinine is gained from processes which may be regarded as due to **Unorganized Ferments.**

Thus the oxidizing action of drawn blood was shown to be diminished in several experiments performed by Binz. For example, it fails to form the blue oxidation product of guaiac, or to decolorize indigo when it is applied to it along with quinine.[1] Or instead of blood a slice of potato or a watery extract of a living plant may be used. The peroxidase of the blood is also rendered less active. From these experiments the inference is drawn that quinine hinders the action of the oxidizing ferments of the blood and tissues. On the other hand, Jacquet found that it had little or no effect on the oxidation of substances passed through the vessels of excised organs. A number of other ferments act more vigorously in very dilute solutions of quinine, while they are retarded by larger quantities; for example, the autolytic ferment of the liver, pepsin and rennet. And some appear to be much less susceptible to its action than others, for they are augmented in activity by quantities that retard or destroy those more readily affected.

These experiments indicate that quinine hinders some, if not all, of the processes which normally occur in living matter, and which are expressed in movement and in various chemical products; they indicate in addition that this action is not confined to the intact protoplasm, but extends to some of the ferments.

Among the **Vertebrates,** also, small quantities of quinine give rise to disturbances of the nutrition, but before discussing these, it may be well to indicate the symptoms induced by poisonous doses.

In the frog a short stage of increased reflex excitability is followed by the loss of spontaneous movements, the arrest of respiration and paralysis of the spinal cord. In mammals the spinal cord is said to be stimulated by small quantities and then to be depressed. The respiration is sometimes accelerated in the beginning, but is afterwards weakened, and its failure is the cause of death. General depression and muscular weakness are usually the only cerebral effects noted, and the tremor and convulsions said to occur in some instances may be due to the use of impure quinine. The heart is often accelerated at first, but is afterwards slow and weak, while the blood-pressure, after a slight increase, declines progressively. According to Santesson, quinine given by the stomach has comparatively little effect on the heart and blood-pressure in mammals. These symptoms point to a preliminary stage of stimulation, followed by depression of the **Central Nervous System** and heart in the vertebrates, corresponding to the two stages observed in the simpler organisms. They are only elicited by very large quantities of the drug and have perhaps received greater attention than they merit at the hands of experimental pharmacologists. The depression of the reflexes of the frog was at one time attributed to a stimulation of the inhibitory centres of Setschenow, and this was supported by the fact that it could be removed at first by division of the medulla oblongata. It seems more probable, however, that the local irritation of the acid salts usually injected caused the temporary depression indirectly, and that the action on the central nervous system consists in a transient stimulation followed by lasting depression. The statement that the depression is due to the weakness of the heart seems incorrect.

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[1] The well-known guaiac experiment is performed as follows: A fresh solution of guaiac resin in alcohol, to which some peroxide of hydrogen has been added, is divided into two parts. To the one a minute quantity of quinine is added, and one or two drops of blood are then allowed to flow into each part. The one containing the quinine remains uncolored, while the other assumes a blue tint from the oxidation of the guaiac by the unpoisoned blood.

The changes in the **Circulation** in mammals are caused by a preliminary contraction of the arterioles and acceleration of the heart, followed by dilation of the former and slowing and weakening of the latter. In both cases the action is probably a direct one on the muscle of the arterioles and heart, although some investigators consider the acceleration due to depression of the inhibitory mechanism in the heart or in the medulla oblongata. The effects of quinine on the isolated frog's heart have been studied carefully by Santesson, who found that the action was entirely muscular and consisted in slowing, accompanied by marked decrease in the strength of the contractions.

In fatal poisoning in mammals the heart is generally very much weakened when the respiration ceases, but continues to beat for some time afterwards.

Quinine acts upon **Muscle** in the same way as upon the simple organisms, temporarily increasing its power and subsequently weakening it. Thus Santesson found that the strength of the individual contractions was increased and that a contraction occurred against greater resistance than normally, but when the stimulation was repeated, fatigue set in sooner than in the unpoisoned muscle. Large quantities of quinine throw the muscle into rigor, which resembles that produced by caffeine, and is probably associated with its action in accelerating the coagulation of myosin (Fürth).

The **Nerve Trunks** are said to be remarkably tolerant to solutions of quinine, which do not lessen their irritability when applied locally in sufficient quantity to cause marked abnormalities in the muscular contraction. No sufficient evidence has been brought forward that quinine affects the peripheral ends of the motor or sensory nerves. The number of **Leucocytes** in the blood is much diminished by the administration of quinine in man and the lower mammals, but it is unknown how this is effected. The statement that the normal **Spleen** undergoes a contraction in size and partial atrophy after quinine, while not improbable in itself, is not supported by experiments in which accurate methods were used.

A slight increase in the amount of **Urine** excreted has been observed sometimes, but does not seem constant. It is attributed to the action of the quinine on the renal epithelium, by which it is excreted. The other secretions do not seem to be altered by quinine, unless it is applied directly to the cells in large quantity by injecting solutions into the duct of the gland. The statement is made that the glycogenic function of the liver is altered so that less sugar than usual is supplied to the blood, and there is some evidence that other hepatic functions are less active than usual.

Cinchona preparations and quinine have the same action on the appetite and digestion in man as the simple bitters and nux vomica. Ordinary therapeutic doses often produce no very obvious symptoms, the most frequently observed effect consisting in derangement of the **Sense of Hearing**, less frequently of that of **Sight**. Ringing or roaring sounds in the ears, accompanied by slight deafness, are produced by moderate quantities and large doses are not infrequently followed by complete loss of hearing for a time. Contraction of the field of vision is observed less often, but in some cases total blindness has been pro-

A bitter tonic for appetite - Often poor hearing & sight even days. Little gi. irrit or pain if subcutaneous. Fullness in head - Confusion. Much used sulph. has been taken (30g) without poisoning.

Idiosyncrasy. Ear ringing skin eruptions, gi. trouble

duced and has lasted for several days or even weeks. Color-vision is especially liable to be rendered imperfect or temporarily paralyzed by quinine; these disorders of sight are accompanied by a very marked contraction and even obliteration of the retinal vessels and sometimes by degenerative changes in the retinal nerve-cells and even by atrophy of the optic nerve. It is still undecided whether the vascular changes or the nervous degeneration is the primary lesion, but the majority of investigators at present favor the view that the constriction of the vessels is merely an accompaniment of the graver effects on the ganglionic structures. The symptoms in the ear have generally been regarded as the result of congestion and hæmorrhages in the tympanum and labyrinth, but Wittmaack has recently shown that this view is founded on erroneous observations, and states that degenerative changes occur in the spiral ganglion in the cochlea exactly analogous to those described in the retina. Quinine possesses some irritant action which betrays itself in discomfort in the stomach and eructation after large and repeated doses by the mouth, and by pain and tenderness when it is injected subcutaneously; but this drawback is not of so much importance as in the case of many other drugs.

Large doses of quinine produce some confusion and depression with a sense of fulness and heaviness in the head from their action on the **Cerebrum**, and this is sometimes accompanied by uncertain gait and slow pulse. Very few cases of fatal poisoning have been satisfactorily determined to be due to quinine, although a considerably larger number have been attributed to it. In these cases marked weakness of the heart and collapse accompanied by loss of sight and hearing, muscular weakness, apathy, slow, gasping respiration and finally unconsciousness and total failure of the respiration were observed. In some cases delirium and convulsions have been noted, but it may be doubted whether the preparation did not contain other members of the cinchona alkaloids. Enormous doses of quinine sulphate have been swallowed without any serious results. Thus in one case thirty grammes (one ounce) produced only some confusion and noises in the ears. Probably only a small quantity of the drug was absorbed, as the sulphate, which is generally used, is exceedingly insoluble.

The extensive use of quinine in therapeutics has demonstrated that many persons have curious **Idiosyncrasies** in regard to it. This is betrayed in many cases by the development of ear symptoms after comparatively small doses, but in others symptoms arise which do not appear in the great majority of people even after large doses. The commonest of these are skin eruptions, of which a large variety have been described, and which can be distinguished from ordinary diseases of the skin only by the history or by the detection of quinine in the urine or in the stools. These exanthemata are often accompanied by some rise in temperature, which has received more attention than it appears to deserve, for it is rare and even when present is of insignificant extent. Other less important effects, which have been occasionally noted, are gastric discomfort and diarrhœa. In very rare

Directly, uterus at term rhythmically contracts

Oxidation of tissues ($O \rightleftarrows CO_2$) OK, but marked lessening of N catabolism

→ So work (heat the same. But growth, repair less

cases the administration of quinine is followed by fever and hæmoglobinuria (black water) or albuminuria; the patients are in almost every case sufferers from old malarial infection, but there is no question that in many cases the symptoms arise only when quinine is given.

The **Uterus** is aroused to contraction by quinine, and abortion occurs occasionally after its use in malaria, while in other cases labor pains may be induced. Many physicians use it during labor if the pains cease or if they seem to be too weak to expel the child. In animal experiments it is found that quinine injected intravenously or hypodermically causes rhythmical contractions of the uterus or strengthens the spontaneous contractions when these are present. The tone of the muscle is also augmented. The exact way in which quinine acts here is unknown, but it may probably be a direct effect on the uterine muscle. The uterus itself is certainly the seat of the action, for it is not prevented by division of the nerves supplying the organ.

In the **Alimentary Tract** quinine and the cinchona preparations act in the same way as the simple bitters (page 54).

The constant effects of quinine on the **Metabolism**, which are produced by quantities of the drug too small to have any further action except in specially susceptible individuals, are of much greater interest and importance than the symptoms already mentioned. This alteration of the tissue change occurs throughout the mammalia, and consists in a marked diminution in the destruction of the nitrogenous constituents of the tissues. After the administration of quinine, the nitrogen in the urine is found at first slightly augmented for a few hours, but then undergoes a diminution of considerable extent, due to a restricted production of all the nitrogenous constituents of the urine, but especially of the urea and uric acid. The phosphates and sulphates undergo a corresponding alteration, but all metabolic changes are not affected, for the carbonic acid exhaled and the oxygen absorbed by the lungs present no marked alteration in amount, so that the oxidation of the tissues cannot be said to be altered, but only the breaking down of the nitrogenous bodies. This absence of effect on the oxidation of the body is not what might have been expected from the experiments of Binz and others on the simpler tissues, for these showed that oxidation of all kinds was retarded by quinine. On the other hand, it corresponds with Jacquet's experiments on the oxidizing ferment of the tissues and has been attested by too many observers to allow of any doubt as to its correctness. In the case of several other drugs the diminution of the urea is compensated for by the increase in the other nitrogenous bodies in the urine, but the fall in the total excretion of nitrogen after quinine points to an alteration of the metabolism of the body in general, and not to the paralysis or destruction of the organs which change the first products of the nitrogenous metabolism to the simpler forms in which they are finally excreted. The oxygen absorbed and the carbonic acid excreted by the tissues are generally held to measure the amount of work done and heat formed by the muscular and other movements of the body,

[illegible] . So when in fever temp is lowered. Not nervous action
~~[illegible]~~ sometimes less radiation to compensate, but therefore, so great drop.
If exciting bugs killed still further tendency to drop in temp.

and quinine therefore does not seem to affect these functions, while it would appear that some other processes, perhaps the death, growth and repair of the tissues, are less active than normally. At any rate, the nitrogenous food is not dissipated so rapidly, but is stored up in the body in some unknown form, for v. Noorden found that under constant diet the nitrogen excretion diminished under quinine and this diminution continued for two days after the treatment was stopped. The nitrogen absorbed from the alimentary canal remained unchanged, and a certain amount of protein food must therefore have been added to the body and saved from the decomposition which it would have undergone in ordinary circumstances.

The influence of quinine on the metabolism is closely connected with its effects on the body **Temperature.** It was early observed that, besides its specific effects in malaria, quinine often depressed the temperature and improved the condition in a number of other fevers. This was long supposed to be due to some action that it exercised on the central nervous system, but when the nervous theory of fever fell into disrepute, this explanation also came to be looked upon with suspicion, and was finally disposed of by the experiments of Binz and others, who showed that quinine lowered the fever temperature after division of the spinal cord. Binz therefore attributed the antipyretic effects of quinine to its direct action on the tissues, and this explanation is generally held to be correct. It is to be remarked that while there is no question as to the reduction of the temperature effected by quinine in many cases of fever, it has little effect upon the normal temperature. In some cases a slight fall in the thermometer is observed, but it is never very considerable, and often no results follow its administration, or a rise of 0.1–0.2° C. may occur.

Gottlieb found that the fever temperature produced in rabbits by injury of the region of the corpus striatum was reduced by quinine, and that the regulation of the heat production according to the temperature of the surrounding air was not impaired by it. Thus, when the temperature of the cage was kept at about 30–32° C., and animals poisoned with morphine and some other drugs had fever temperature, the rabbit to which quinine had been administered showed little change from the normal. From this he infers that the heat-regulating mechanism of the brain is not affected by quinine, and that the reduction of temperature, when it occurs at all, is due to alteration in the metabolism. In a later research the same author found by calorimetric experiments that the warmth production was lessened by quinine, both in normal animals and in those in which fever had been induced by injury of the corpus striatum. This lessened production was accompanied in Gottlieb's experiments by a fall in the output of heat, the regulating apparatus tending to counterbalance the reduced formation in the same way as in normal animals. In other experiments, however, quinine has been found to induce dilatation of the skin vessels and a corresponding increase in the heat loss. In other words, quinine appears to lessen the heat formation through its action on the tissues, and this is sometimes compensated for by a decrease in the heat loss, but in other instances the regulation fails and the temperature falls from the formation being lessened and the loss remaining unchanged or even being increased.

This explanation of the antipyretic effects of quinine is not without difficulties, however. For the chief source of heat in the body is the oxidation of the carbohydrates, but in healthy animals quinine does not lessen the amount of carbonic acid excreted, as it might be expected to do if it reduced the heat formation by restricting the combustion in the tissues. Some writers, therefore, hold that the fall in temperature is really the effect of dilatation of the skin vessels and increased heat loss. This explanation is not that generally accepted, however, and while it is not denied that the augmented output of heat may in some conditions contribute to the fall in temperature, the antipyretic action of quinine is still regarded as due for the most part to its retarding the metabolism; it has been suggested that while the combustion in the normal tissues is not affected by quinine, the presence of fever poisons throws them into a state of augmented activity in which they are more susceptible to its sedative action, and that even in the normal organism a reduction of the temperature might be induced if sufficient of the drug could be ingested without exciting other symptoms. In this connection it is of interest to remember that in fever the nitrogenous decomposition is much increased, while quinine has a directly opposite effect. The diminution in the nitrogenous metabolism may also lead to an increased resistance being offered by the tissues to the cause of the fever, or may lessen the poisonous products circulating in the blood. In addition, the microbes of fever may themselves be rendered less active by the drug, although this antiseptic action would appear to be of subordinate importance, as many of the pathogenic forms have been found to offer great resistance to it.

Fig. 54.

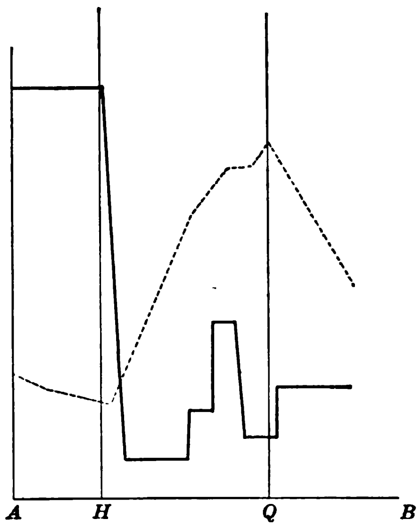


Diagram to illustrate the relation of the warmth output and internal temperature (after one of Gottlieb's experiments). The unbroken line represents the changes in the warmth output, which may be estimated by measuring its distance from the abscissa *AB*. The dotted line represents the internal temperature. From *A* to *H*, normal. At *H* an injury to the brain caused a marked diminution in the heat output and a corresponding rise in the internal temperature. At *Q* quinine was administered and was followed by an immediate fall in the internal temperature, while the heat output was practically unchanged. Contrast Fig. 56.

Quinine has much more effect in reducing temperature when it is

Quinine lowers temp best at period of natural remission - (as other antipyretics) 1/3 absorbed in urine. Rest burned. Other alkaloids in large doses tend to convulsions.

administered in the beginning of a natural remission than when it is given during a rise of the thermometer. This property is shared by most antipyretics and will be treated of at greater length under the antipyrine series.

Excretion.—Quinine appears in the urine within a short time (30 minutes) after its exhibition by the mouth, and it continues to be excreted by the kidney in some quantity during the next twenty-four hours, and in smaller amounts up to about seventy-two hours. Only about one-third of that absorbed appears in the urine, however, and none whatever has been found in the other excretions, so that from two-thirds to three-fourths undergoes complete destruction in the tissues. In man quinine appears unchanged in the urine, while in the dog the small proportion excreted has undergone extensive alteration in the tissues.

Of the **Other Cinchona Alkaloids**, quinidine or conquinine resembles quinine most closely in its effects, which are somewhat weaker, however. Cinchonine, while very similar to quinidine in most points, has some tendency to produce convulsions, but this effect is much more liable to occur under cinchonidine which, save for its resemblance in other features to quinine, would be entitled to be classed among the convulsive poisons. These convulsions are of an epileptiform character, and are only produced by very large doses, but Albertoni discovered that even small quantities administered to epileptics increased the number of the attacks. He found that these epileptiform seizures were not prevented by the removal of the cerebral cortex in dogs, and that the irritability of the motor areas was not altered by cinchonidine, and therefore concluded that the poison produced these symptoms by acting on some lower division of the central nervous axis. It is believed by many, however, that epileptic attacks can be elicited only when the cerebral cortex is intact, and although no results directly opposed to those of Albertoni have been recorded, the question must still be regarded as an open one.

In other respects cinchonine and cinchonidine differ from quinine only in the degree and not in the kind of their action. Cinchonamine possesses an even more marked convulsant action than cinchonidine.

The effects of the other alkaloids have not been the subject of much investigation, but they seem to differ from quinine chiefly in their effects on the central nervous system. These are not entirely absent in quinine itself, for, as has been stated already, the reflex irritability is at first increased and then diminished in both frogs and mammals, and in some cases even convulsions are stated to have occurred in quinine poisoning, although these are so rare that the suspicion is aroused that the preparation was contaminated with cinchonidine or some other alkaloid.

Cinchonidine seems the most poisonous of the four chief alkaloids, quinine following next, and then cinchonine and quinidine.

PREPARATIONS.

U. S. P.—**Cinchona**, the bark of Cinchona calisaya and of C. officinalis and of hybrids of these and of other species of Cinchona, yielding not less than 5 per cent. of total alkaloids. Dose, 1 G. (15 grs.). 1 g

Cinchona Rubra, red cinchona, the bark of Cinchona succirubra, containing at least 5 per cent. of alkaloids. Dose, 1 G. (15 grs.).

Fluidextractum Cinchonæ, contains 4 per cent. of quinine, quinidine and cinchonidine, 1 c.c. (15 mins.). 1 cc

TINCTURA CINCHONÆ, contains 0.75 per cent. of these alkaloids, 4 c.c. 4 cc (1 fl. dr.).

Quinine prep. .3-1.3 Tinct cinchona 4 c.c.
Give in capsules to disguise bitter

Tinctura Cinchonæ Composita is the only preparation of red cinchona, and contains in addition serpentaria and bitter orange peel. 4 c.c. (1 fl. dr.).

These preparations of cinchona were formerly much more in vogue than at the present day, in which they have been replaced for most purposes by the alkaloids. They are still prescribed alone or together with other remedies as stomachic bitters.

Quinina, insol
Quininæ Sulphas, insol
Quininæ Bisulphas, 10 pts sol — 0.3–1 G. (5–15 grs.); to be increased when necessary. .3-1.G
Quininæ Hydrobromidum,
Quininæ Hydrochloridum, more sol 35
Quininæ Salicylas (U. S. P.),
Ferri et Quininæ Citras, 0.25 G. (4 grs.).
Ferri et Quininæ Citras Solubilis, 0.25 G. (4 grs.).
Syrupus Ferri, Quininæ et Strychninæ Phosphatum, Easton's syrup, 4 c.c. (1 fl. dr.). + cc
Elixir Ferri, Quininæ et Strychninæ Phosphatum, 4 c.c. (1 fl. dr.).
Glyceritum Ferri, Quininæ et Strychninæ Phosphatum, 1 c.c. (15 mins.).
~~*Cinchoninæ Sulphas,*~~ — 0.25 G. (4 grs.). .25G
Cinchonidinæ Sulphas,

B. P.—**Cinchonæ Rubræ Cortex**, red cinchona bark, the dried bark of the stem and branches of Cinchona succirubra. It ought to contain 5–6 per cent. of total alkaloids, of which one half should consist of quinine and cinchonidine.

Extractum Cinchonæ Liquidum, 5 per cent. of alkaloids, 5–15 mins.
Tinctura Cinchonæ, 1 per cent. of alkaloids, ½–1 fl. dr.
Tinctura Cinchonæ Composita, containing bitter orange peel, serpentary and coloring matters, ½–1 fl. dr.
Infusum Cinchonæ Acidum, containing aromatic sulphuric acid, ½–1 fl. oz.
Quininæ Hydrochloridum, — 1–10 grs.
Quininæ Hydrochloridum Acidum,
Quininæ Sulphas,
Tinctura Quininæ, formed from the hydrochloride and flavored with orange, ½–1 fl. dr.
Tinctura Quininæ Ammoniata, formed from the sulphate, ½–1 fl. dr.
Vinum Quininæ, ½–1 fl. oz.
Pilula Quininæ Sulphatis, 2–8 grs.
Syrupus Ferri Phosphatis cum Quinina et Strychnina, Easton's syrup. Each fl. dr. contains $\frac{1}{8}$ gr. of quinine sulphate and $\frac{1}{32}$ gr. of strychnine. ½–1 fl. dr.
Ferri et Quininæ Citras, 5–10 grs. (See Iron.)

Quinine is practically insoluble in water and several of its salts are only dissolved sparingly. Thus, the sulphate requires 800 times its own weight of water, the hydrochloride 35, and the hydrobromide 54. The presence of acid in excess renders them much more soluble, and the acid hydrochloride is dissolved in less than its own weight of water, the bisulphate in 10 parts. They all form crystalline powders with a very bitter taste, and their solutions in water have a blue fluorescence when sulphuric acid is present. The acid hydrochloride and the bisulphate have an acid reaction, the others are neutral.

The sulphate of quinine is the salt generally prescribed, although the hydrochloride is more soluble and ought to be preferred. The hydrobromide is comparatively seldom used. Instead of the acid salts being prescribed, some sulphuric acid or hydrochloric acid may be ordered to be added to the neutral salts in order to facilitate their solution.

The salts of quinine are frequently given in the form of pills, cachets, tablets, or capsules, which have the advantage of avoiding the bitter taste, but from which the alkaloid is more slowly absorbed than from solutions. Care must be taken that the pills are soft and freshly prepared, as when kept for

Warburg's tincture a shotgun prescription for malaria.

any length of time they become hard, and in this condition frequently pass through the bowel unabsorbed. The salts or the pure alkaloid may also be given as powders, or the former in solution, but these are objected to by many patients on account of the bitter taste. When a rapid absorption is desired, solutions should be used, flavored, if necessary, with syrup and volatile oils. Solutions of the salts are occasionally injected as enemata, but are liable to set up irritation and be rapidly evacuated. The hypodermic method has also been advised in cases of emergency, or where the salt cannot be retained or absorbed from the stomach; for this purpose a solution of the hydrochloride with hydrochloric acid in excess or of the sulphate is injected deeply into the muscular tissue. This form of medication is painful, but does not seem to induce more serious results if ordinary care is used. The neutral hydrochloride may be dissolved in hot water and injected when the solution reaches the body temperature with less pain than is elicited by other salts. In this way about two parts of water are required to dissolve one of quinine. The addition of urea to the solution renders it less irritant. Quinine is very easily dissolved in water when it is mixed with antipyrine in the proportion of three parts of quinine to two of antipyrine, and this solution is said to be less painful when it is injected hypodermically than others. The intravenous injection of quinine has been practised by Baccelli with success in cases of pernicious malaria. He uses the hydrochloride in a solution of common salt and injects into one of the veins of the arm.

Many other salts of quinine have been proposed and have enjoyed a certain reputation for some time. Among the better known of these is the *tannate,* which is exceedingly insoluble and almost tasteless, and is prescribed in powder in doses of 1–3 G. Other salts which have been recommended are the *tartrate* and the *lactate. Euquinine* is the ethyl-ester of quinine-carbonic acid $(CO(OC_2H_5)(OC_{20}H_{23}N_2O))$ and is said to possess the therapeutic virtues of quinine without its bitter taste and without inducing ringing in the ears and other symptoms. *Aristochine* $(CO(C_{20}H_{23}N_2O)_2)$ and *Chinaphenine* $(CO(NH \cdot C_6H_4 \cdot OC_2H_5)(OC_{20}H_{23}N_2O))$ are compounds of quinine of a similar nature recently introduced. All three preparations are prescribed in powder or tablets, in the same dose as quinine.

A famous preparation of quinine is *Warburg's tincture,* which has been extensively used in India in the treatment of malaria. It contained a very large number of ingredients, many of which were certainly entirely superfluous. Among the more important constituents were aloes, rhubarb, gentian, camphor and various volatile oils; it is possible that some of these may have aided the quinine through their effects on the stomach. Various drugs, such as capsicum and piperine, have long had some reputation as adjuvants in quinine treatment for a similar reason.

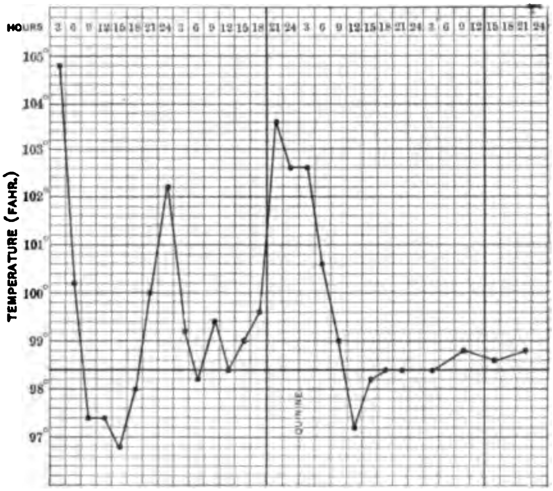
The other alkaloids have been used occasionally as substitutes for quinine, but have somewhat less therapeutic effect, while cinchonidine is more liable to produce symptoms of poisoning. They might all be dispensed with, without loss to therapeutics.

Therapeutic Uses.—The introduction of cinchona into therapeutics was due to the discovery of its efficacy in ague or **Malaria**, and with growing experience in the disease and its treatment, the confidence in the drug, or rather in its chief alkaloid, has constantly increased, until the action of quinine in malaria is now quoted as the best example of a specific in therapeutics. The explanation of its action has only been arrived at within the last few years with the discovery of the cause of malaria, the plasmodium malariæ, although in 1868 Binz suggested that the then unknown malarial poison was probably rendered inert by quinine. The plasmodium belongs to the group of

The malaria protozoa specifically killed. Resistant ones remain & treatment must be continued. Malaria or ague. Plasmodium malariae. Acts best after or just before paroxysm when in amoeboid form least resistant.

protozoa, and in one of its stages comes to resemble somewhat the amœba, on which Binz experimented. The effect of quinine seems similar in the two organisms, although the alkaloid acts more strongly on the malarial organism in the blood than on the common amœba living in water; another organism closely related to that of malaria and found in the blood of birds appears to be unaffected by quinine. When quinine is administered to a patient suffering from malaria the organism in the blood breaks up and disappears, leaving only a few more resistant forms; these, however, may continue to grow and multiply until they cause a second attack, unless the treatment be continued and the surviving organisms, changing into less resistant forms, are destroyed by the drug.

FIG. 55.



Temperature chart in a case of malaria in which quinine (10 grains) was administered in the third paroxysm as the temperature was falling. On the following day no rise of temperature occurs. The temperature was taken every three hours. (DOCK.)

In a drop of malarial blood the plasmodia may be seen in active movement, but a minute drop of quinine solution paralyzes and kills them, exactly as it kills the amœba. The explanation of the action of quinine on malaria lies in its effects as a protoplasmic poison, therefore, which acts more strongly (specifically) on the protozoon which is the cause of ague, and can consequently be introduced into the human body with impunity in doses which are destructive to the simpler organisms which have invaded it. Experience has shown that quinine is most effective when it can act immediately after the paroxysms of ague, and this is now explained by the fact that the organisms are in their least resistant form—the amœboid—at this time. If quinine is given at the beginning of an attack, sufficient will remain in the blood when the temperature begins to fall to destroy the unprotected spores of the parasite, or the same result may

15 then 15 every [illegible] days. Bitter taste, & vomiting sometimes indicates. In suppositories or intramuscularly & weekly doses for prophylaxis. Reduces size of spleen - removes cause. By reducing leucocytes may be good in leukaemia. In other fevers less danger of collapse than other antipyretics acts longer

be obtained by a dose given as the temperature begins to fall, provided the drug is rapidly absorbed, as is ordinarily the case. It may be ordered in one dose of about 1 G. (15 grs.), or in divided doses given at intervals during the fall of the temperature. This frequently prevents the next attack, but if any rise of temperature occurs, a smaller dose should be administered. After this a dose of 1 G. should be given every six days, in order to complete the destruction of the organisms which have developed from the resistant forms left alive after the first administration. Quinine is generally administered by the mouth in malaria, but its intensely bitter taste renders this treatment disagreeable, and in children and in cases of persistent vomiting it may be impossible; in such circumstances it may be given in an enema or suppository, or in children the tasteless forms may be employed. In recent years good results have been obtained by the hypodermic method, and in the severe form known as pernicious malaria, Bacelli found the intravenous injection superior to any other method of administration. A great deal of weight was formerly laid on the use of purgatives and emetics as preliminaries to the treatment of malaria with quinine, and the former are undoubtedly of service sometimes, although it is unnecessary to delay the quinine treatment by waiting for the intestines to be evacuated.

Quinine is used not only as a remedy, but also as a prophylactic against malaria. Its value for this purpose has been attested by long experience, but there is still no unanimity of opinion as to the best method of administration and the dose required. Plehn found that one gramme of the sulphate given in one dose every seven days was sufficient to prevent the disease, which is believed to have an incubation period of a week, while others recommend doses of 0.1–0.2 G. (2–3 grs.) every morning.

One of the results of quinine medication in early cases of malaria is the reduction of the enlarged spleen, and this has led to its use in other **Diseases of the Spleen** with enlargement. In malaria the effect on the spleen is only secondary to the removal of the cause of the disease, but the action of quinine in lessening the number of leucocytes in the blood might explain some alteration in the spleen. In some cases of leucæmic enlargement encouraging results have been obtained from the continued use of quinine.

Various other **Febrile Conditions** have been treated with quinine, partly for the sake of its antipyretic effects and partly in the belief that it acts as an antiseptic in the blood. As regards its effect on the temperature in non-malarial fever, it not infrequently causes a considerable fall, and has the advantage of possessing a more prolonged action and of causing less risk of depression and collapse than the newer antipyretics. On the other hand, the fever is not reduced so rapidly and generally not to the same extent as by the latter, and the large quantities of quinine required are liable to cause discomfort from their effects on the brain and hearing. Typhoid fever, scarlatina and other acute pyrexias are sometimes treated with quinine for

Benefit lies in lessened N metabolism. If enough given to destroy microbes, will probably destroy body tissues. In neuralgia & headache why? Bitters. Of doubtful value in whooping cough, hay fever, influenza, &c.

this effect. The best results are obtained when it is exhibited in maximal doses when the temperature is falling or when it has been temporarily reduced by other means, such as cold baths. Perhaps, however, the beneficial action of quinine in those cases ought to be measured not so much by the reduction of the body temperature as by the lessened destruction of the tissues. It would be interesting to know whether in those cases in which quinine treatment is successful, the nitrogen of the urine is diminished in proportion to, or in excess of the fall of the temperature. In general, antipyrine and its allies have succeeded in ousting quinine from its former position as the best of the antipyretics. The use of quinine has been recommended in septicæmia, largely from a belief in its antiseptic action in the blood. In this connection it is to be remarked that the microbes of septic fever are very much more resistant to the action of quinine outside the body than are the protozoa, and the question therefore arises whether the blood and tissues are not liable to be seriously injured by the quantity of quinine required to act on the parasites they contain. In many cases of septicæmia in which beneficial results are said to have been obtained by the use of quinine, the quantity administered was obviously too small to have any effect either on the temperature or on the microbes.

Quinine has been used in various forms of **Neuralgia and Headache,** especially when they were periodic in their appearance, and good results have been obtained in these cases and also in others where no periodicity could be observed. Many of these were certainly not of malarial origin, and no explanation of the action of quinine here has been proposed. Perhaps the lessened formation of uric acid and other poisonous products may be suggested as a possible cause of the improvement.

The tinctures of cinchona are often prescribed as **stomachic bitters** and for this purpose are generally fortified by preparations of nux vomica or of the simple bitters.

Quinine has been advised in whooping-cough, hay fever and influenza, and in fact is regarded by many as a specific in these diseases, though others have found it unreliable. It is often difficult to induce a child to take the bitter salts, and recourse may be had to the alkaloid itself, euquinine, or the tannate disguised with sugar or chocolate. The use of a solution as a wash for the nose in hay fever was brought into prominence by Helmholtz, who gained relief in this way, but it has not proved very efficacious. The local use of quinine solutions and of cinchona preparations is also advised in relaxed throat (gargle) and in gonorrhœa (urethral injection). It has sometimes been used as an antiseptic externally, but is too expensive for ordinary use.

Quinine has been advised as an **ecbolic** to increase the contractions of the uterus during labor. This was suggested by the observation that in malarial regions, abortion occasionally occurred after quinine, and many observers report the most satisfactory results from the

[illegible] at term. Contra-indic:– Idiosyncrasy. [illegible]
[illegible] or vision disturbance. (Give K Br). In gi: irrit. give. hy-
po. May aggravate condition if given to a weak patient with
[illegible] fever. If haemoglobinuria give no more. Pregnancy not at term is no danger

treatment of uterine inertia with one-gramme doses of quinine, and prefer it to ergot in this condition. The movements of the uterus induced are practically identical with those occurring naturally.

Contra-indications.—Where a special idiosyncrasy exists, quinine may be unsuitable, but these cases are far rarer than is generally believed. A moderate action on the hearing, for example, is not to be considered a contra-indication, although in those cases a small dose is often found sufficient in malaria. Where an inflammatory condition of the membranes of the ear already exists, quinine ought to be administered with care, or avoided entirely if possible. The addition of bromides is often found to lessen or remove the discomfort arising from the disordered hearing, but the quantity of bromide contained in the hydrobromate of quinine is insufficient to effect this, and the ordinary potassium salt ought therefore to be prescribed. Where very marked disturbance of the digestion exists, quinine is often liable to augment it, owing to its irritant properties, and must therefore be given with caution by the mouth, or perhaps is better applied hypodermically. Hæmoglobinuria following the administration of quinine, of course, contra-indicates its further use. Abortion so seldom occurs after quinine that pregnancy is no objection to its administration. In general, it may be stated that quinine is often credited with many disadvantages which it does not possess, and that in cases of malaria, in which it is practically without a rival or substitute, only the most pronounced idiosyncrasy can justify withholding it. In other cases, as in septic fever, it may be a question whether it does not aggravate the condition when it is administered to very weak patients.

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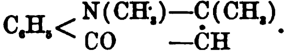
XXVIII. THE ANTIPYRETICS. (ACETANILIDE AND ANTIPYRINE SERIES.)

The antipyretics are a very recent addition to therapeutics, the oldest of this group now in use dating only from 1884. Up to 1875 the only means of combating high temperature were baths, vegetable alkaloids, such as quinine and aconitine, or alcoholic preparations, but in that year Buss discovered that salicylic acid produced a fall in the fever temperature, and soon afterward carbolic acid and resorcin and its isomers were employed as antipyretics. A very large number of antipyretics have been introduced since that time, but most of them have had only a temporary vogue, and those in general use at the present time are comparatively limited in number.

Quinine is a quinoline derivative, and quinoline itself, as well as some of its simpler compounds, were among the earlier antipyretics suggested. *Quinoline* (C_9H_7N) was soon found to be dangerous from its producing collapse, but its derivatives *Kairine* ($C_9H_9(OH)N{-}C_2H_5$), *Kairoline* ($C_9H_9(CH_3)(OH)NH$) and *Thalline* ($C_9H_9(OCH_3)NH$) were used extensively, although they have now been almost entirely abandoned. In fact the only quinoline bodies now used as antipyretics are *Analgen* and *Thermifugine,* which are still prescribed to a limited extent.

A new antipyretic was introduced in 1884 under the name of **Antipyrine,** which is derived from phenylhydrazine, and has proved superior to all of the earlier drugs. *Phenylhydrazine* ($C_6H_5{-}NH{-}NH_2$) produces a fall in the fever temperature, but this is frequently accompanied by collapse and changes in the blood, which prevents its use in medicine. Several of the simpler compounds, such as *Pyrodine* (acetylphenylhydrazine) and *Antithermine* (phenylhydrazine and lævulinic acid), have received a more or less extensive trial as antipyretics, but have proved dangerous and inferior to *Antipyrine,* phenyldimethylpyrazolon,  $C_6H_5{<}\begin{matrix}N(CH_3){-}C(CH_3)\\ CO\quad{-}CH\end{matrix}$. The latter is still very largely used as an antipyretic, either in its original form or as a constituent of numerous combinations which have been introduced of late years. Among these may be mentioned *Resopyrine* (resorcin and antipyrine), *Hypnal* (chloral and antipyrine), *Salipyrine* (salicylic acid and antipyrine).

Antipyrine early found a rival in **Antifebrine** or **Acetanilide,** which was advised as an antipyretic in 1886 by Cahn and Hepp. *Aniline* ($C_6H_5NH_2$), from which it is derived, has also some action on the temperature, but like phenylhydrazine produces dangerous collapse and destruction of the blood cells. Acetanilide ($C_6H_5NHCOCH_3$), the first of its derivatives to be introduced, is not entirely devoid of this poisonous action, and has been supplanted to a considerable extent by more complex and less poisonous bodies. One of these, *Exalgine* ($C_6H_5NCH_3COCH_3$), differs from antifebrine only in possessing a methyl group in the side chain, and seems to resemble it closely in its effects. Another which enjoyed a short trial is *Benzanilide* ($C_6H_5NHC_7H_5O$), in which the acetyl radicle of antifebrine is replaced by benzoyl. It was soon found that both aniline and antifebrine underwent a partial oxidation in the body, with the formation of amidophenol or its derivatives, and the belief that the antipyretic effects were due not so much to the original substance as to these oxidation products led to the introduction of numerous derivatives of paramidophenol $\left(C_6H_4{<}\begin{smallmatrix}OH\\NH_2\end{smallmatrix}\right)$. This body has antipyretic properties but suffers under the same disadvantages as aniline. Among its derivatives the most satisfactory antipyretics are those in which the hydrogen of the hydroxyl is substituted by an alkyl, while an acid radicle is added to the amido-radicle. The first of its compounds to be introduced was **Phenacetine** $\left(C_6H_4{<}\begin{smallmatrix}NHCOCH_3\\OC_2H_5\end{smallmatrix}\right)$ which differs from antifebrine only in the addition of ethoxyl in the para position. *Methacetine,* which resembles phenacetine in all points save in methoxyl being substituted for ethoxyl, appeared about the same time. Phenacetine was found to be much less dangerous than acetanilide and antipyrine, and has therefore been largely used, and has been followed by other bodies which are identical with it, except in the acid radicle attached to the nitrogen. Among these phenetidines may be mentioned *Lactophenine* (lactyl-phenetidine), *Malakine* (salicyl-phenetidine), and *Saliphen* and *Salophen,* which contain similar constituents, *Apolysine* and *Citrophen* (citryl-phenetidine), *Kryofine* (methylglycolic-phenetidine), and *Phenocoll* (glycocoll-phenetidine), with its compound with salicylic acid, *Salocoll.*

Several urethane derivatives have also received a trial as antipyretics, among them being *Euphorine* (phenylurethane), which is somewhat poisonous, *Thermodine* (phenacetine-urethane), and *Neurodine* (acetoxyphenylurethane).

With the exception of antipyrine and the quinoline compounds, all the antipyretics at present in use probably owe their activity to the formation of simple derivatives of paramidophenol in the tissues, and differ chiefly in the rapidity with which this decomposition occurs. A rapid formation of paramidophenol produces destructive blood changes and a tendency to collapse, while the antipyretic effects pass off very rapidly. Those drugs are found the most satisfactory antipyretics in which the decomposition proceeds gradually, so that the temperature falls slowly and remains low for a longer time. The simpler antipyretics, such as antifebrine, have given way largely therefore to the phenetidine compounds.[1] Among these it is impossible to determine the most suitable antipyretic, but none of them has been proved to be superior to phenacetine. Where the merits seem so equally divided, it is perhaps more important to learn to use one with judgment than to hurry after each new product without sufficient experience of its predecessor.

Symptoms.—The effects of the antipyretics vary not only with the dose but with the individual patient. Many persons can take very large doses without apparent effect, while in others comparatively minute quantities produce symptoms of greater or less importance. The effects are not always the same, even in one individual under the same dose of the antipyretic, and it is impossible to state at present what are the conditions that involve the peculiar train of symptoms. A very large number of disorders have been attributed to the antipyretics in man, but it is impossible to consider any here except those more commonly observed. Among these are *skin eruptions* of various forms, such as red, erythematous, itching patches or more widely diffused hyperæmia resembling the onset of measles or scarlatina; urticaria occurs not uncommonly, while eczema and bullæ are rarer. In some cases an œdematous swelling has been observed. Some *fever* occasionally accompanies the eruption and renders the diagnosis from the infectious exanthemata even more difficult. These skin affections seem to be elicited more frequently by antipyrine than by antifebrine and the phenetidine compounds. They have been attributed to dilatation of the cutaneous vessels, but this in itself is insufficient to explain their appearance, although it may be a favoring condition. Profuse *perspiration* not infrequently follows the use of the antipyretics in fever, and if the fall in temperature be rapid, and the action of the drug passes off soon, the subsequent rise of temperature may be accompanied by *shivering and rigor,* but these symptoms are scarcely to be looked upon as direct effects of the drug, but rather as resulting from the rapid changes in temperature. They are produced much more frequently by the older and simpler antipyretics than by those of more recent introduction.

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[1] For a detailed discussion of these principles see *V. Mering,* Therap. Monatsch., 1893, p. 577, and *Hinsberg & Treupel,* Arch. f. exp. Path. u. Pharm., xxxiii., p. 216.

Sometimes *catarrh,* burning and swelling *of the throat* and *mouth* are observed after antipyrine, and more rarely *nausea* and *vomiting.* *Cerebral symptoms* are rarely elicited beyond slight dulness, confusion or apathy. Alterations of the hearing similar to those described under quinine have been observed in some cases. More serious symptoms are those of *collapse,* which are occasionally produced in susceptible persons, especially by large doses. Antifebrine is much more liable to elicit these than antipyrine, which in turn is more dangerous than phenacetine and the other phenetidine derivatives. In the milder cases of collapse the skin is cool, the pulse is rather small and rapid, and some anxiety and alarm is felt by the patient, but the condition passes off in a short time. In more severe cases the skin is cold and covered by a clammy perspiration, the heart is weak, irregular and sometimes fluttering, the temperature may be subnormal and the pupils are slightly dilated. The patient may be conscious, fainting may occur, or an apathetic, confused condition may be produced. The weakness of the heart is the chief source of anxiety, and the total failure of the circulation seems to be the cause of death. These cases of collapse occur more frequently when a rapid fall of temperature has been produced than under other circumstances, but may be observed in cases in which no fever has been present.

Marked *cyanosis* occurs occasionally under all the antipyretics, but more frequently under antifebrine and the earlier members of the series than under antipyrine and the phenetidine compounds. Its chief cause appears to be the formation of methæmoglobin in the blood, although it is said to have been present in some cases in which this pigment could not be recognized, and it is often more intense than that observed from the action of other poisons which lead to the formation of methæmoglobin; this suggests that, in some cases at least, the cyanosis arises from feebleness of the circulation rather than from changes in the blood pigment. It is often accompanied by dyspnœa and acceleration of the pulse, and it lasts for a varying length of time, sometimes passing off in a few hours, at other times persisting for several days.

Occasionally a certain *tolerance* is gained, and larger doses of the antipyretics are required to produce effect than were necessary at the beginning of the treatment. A few cases of *chronic poisoning* are recorded from the habitual use of acetanilide. The symptoms consist in disturbance of the digestion, cyanosis, tremor, muscular weakness and general mental debility; the blood is often chocolate colored from the formation of methæmoglobin, and the urine often contains hæmoglobin, or its products, or may be colored by the oxidation products of paramidophenol. The condition is sometimes difficult to recognize, especially as the patient may deny that the drug has been taken. The symptoms disappear rapidly when the drug is given up, but the sudden withdrawal may cause acute mental symptoms similar to those induced in morphinomaniacs when the administration of morphine is stopped too suddenly.

These drugs are by no means very poisonous, normal animals showing no reaction to doses which are sufficient to cause marked changes in fever. In the frog **Antipyrine** causes an increase in the reflex irritability, which sometimes leads to tetanic convulsions and is followed by depression, loss of the voluntary movements, and eventually by complete paralysis and death. In mammals its injection is followed at first by a period of quiet and sometimes of somnolence, which is said by some authors to occur also in the frog previous to the increase in the reflex irritability. Some rise in the reflex irritability may be made out in the mammal at this stage, and large doses cause convulsions and tremors, and subsequently unconsciousness and collapse, ending in complete paralysis. The pulse is accelerated by small doses, while in the later stages of poisoning it may be slow, and some dilatation of the skin vessels and flushing have been observed. The respiration is at first accelerated, and then becomes slow and irregular when large doses are injected. In dogs vomiting and dilatation of the pupil generally occur.

Antifebrine is more poisonous than antipyrine in both frogs and mammals, but resembles it in its general effects, producing first a more or less marked stage of lessened activity, followed by convulsive movements. The respiration is not so much accelerated as by antipyrine, and, according to some observers, is slow from the beginning of the action. The heart is first accelerated and then slow and irregular, and cyanosis and collapse are more frequently observed than under antipyrine. **Phenacetine** and its allies are much less poisonous than the two foregoing, but in large quantities produce almost identical effects—somnolence followed by convulsions, cyanosis and collapse symptoms, first rapid, then slow respiration and heart. **Analgen,** which may be taken as a type of the quinoline derivatives, acts in a very similar way to the others, and is more toxic than phenacetine, and, according to some writers, than antipyrine. Some depression of the spontaneous movements and of the reflexes is described as following its administration to mammals, and large doses produce convulsions and cyanosis. **Lactophenine** is said to have a more sedative effect than the other antipyretics, and to induce complete narcosis in the rabbit.

Action.—The action of these drugs on the various organs is very imperfectly understood. The **Nerve Centres** are affected, as is shown by very slight somnolence occasionally in animals and also in man, but much more frequently by the relief of pain as in neuralgia and headache; this is generally attained without any observable depression of mental activity and is therefore quite distinct from the analgesia obtained by the use of morphine or anæsthetics. This suggests that the antipyretics relieve pain by affecting some point lower than the cerebral cortex, which may be assumed to be a synapse on the path conveying pain sensations; there are two of these, one in the spinal cord and one in the thalamus, and as the antipyretic action of this group is due to changes in the thalamus, it seems likely that their action in abating pain may be located here also (Head). Most of the antipyretics increase the excitability of the spinal cord at first, and this may lead to convulsions in the frog. The origin of the convulsions in mammals is still somewhat doubtful; in general, they seem to be of cerebral origin, but when large quantities are injected they are seen even when the spinal cord is divided from the brain, so that the cord appears to be thrown into a condition resembling that discussed under strychnine poisoning. In considering the cause of these convulsions perhaps too little weight has been laid by some writers on the changes in the blood, respiration and circulation, for it is possible that the convulsions in some cases are asphyxial in character, and not due to the direct action of the poisons on the brain. In ordinary poisoning the peripheral **Nerves** and nerve ends do not seem to be seriously involved, and the final paralysis in both frogs and mammals is undoubtedly central. Santesson found that antipyrine tended to increase the power of the frog's **Muscles**, and several observers have noted that the nerves and motor terminations are paralyzed by the direct application of this drug. Antipyrine has some effect as a local anæsthetic when applied to the mucous membranes.

The **Heart** in the frog and mammals is first accelerated and then slowed by the antipyretics in general, these alterations being entirely independent of the inhibitory mechanism and due to a direct effect on the cardiac muscle. The increased rhythm of the heart leads to a slight rise in the blood-pressure, which sinks again as the pulse becomes slower. There is no satisfactory proof that the vaso-motor centres are involved in the rise of pressure, although it is not unlikely that they undergo a primary stimulation at the same time as the respiratory centre. The vessels are said to be dilated by the perfusion of antipyrine solutions, but it seems improbable that this plays any rôle in ordinary methods of application.

Most of this series except antipyrine and its compounds tend to cause alterations in the **Red Blood Cells** when they are given in large quantities. This action is manifested especially by the simpler bodies of the series, and is still more marked in poisoning from aniline, phenylhydrazine, paramidophenol or quinoline. On the other hand, most of the phenetidine compounds produce it much more rarely, and antipyrine seems devoid of this action. The alteration consists in the formation of methæmoglobin, which may be readily detected by its characteristic spectroscopic appearance. Small quantities of the antipyretics cause its formation within the blood-cells, which remain intact, but larger doses, especially of the more poisonous members, destroy the red blood cells and free the methæmoglobin in the plasma. In the blood various distorted, shrunken red cells may be observed, often entirely devoid of coloring matter, while part of the methæmoglobin seems to escape through the kidneys, and nephritis occurs in some cases with albumin, hæmoglobin and even blood in the urine. This effect on the blood seems due to the decomposition of the antipyretics and the flooding of the tissues with paramidophenol, or the corresponding quinoline derivative. This decomposition proceeds more slowly in phenacetine and its allies and is absent after antipyrine, which explains the rarity of the symptoms after these drugs. When the antipyretics are added to blood outside the body no methæmoglobin is formed, as this effect arises only from their decomposition products.

All of the antipyretics have some **Antiseptic** action, which varies in the different members with their solubility and stability. Antipyrine is found to preserve blood from putrefaction for some days when added to it so as to form a solution of 2–5 per cent. Watery solutions of this strength destroy protozoa and stop the movements of the leucocytes, but antipyretics administered to the higher animals have no such effect on the emigration of the leucocytes from the vessels as is seen under quinine.

The action of the antipyretics on the **Metabolism** of healthy men and animals has been the subject of a number of investigations which have given by no means uniform results, especially in regard to the nitrogen elimination. *Antipyrine* has no influence, or only an insignificant one, on the metabolism of the healthy tissues, whether this be measured by the nitrogenous excretion or by the gaseous exchange in the lungs.

Antifebrine, on the other hand, has a distinct effect on the nitrogen eliminated, although this is only elicited by large doses. After ordinary quantities the urea and total nitrogen of the urine may be slightly augmented, but in large doses antifebrine causes an increase of 30–35 per cent. in these, which indicates a large increase in the tissue waste. The *other antipyretics* have not been examined so carefully. Thalline is said by Kumagawa to increase the nitrogen eliminated like antifebrine, while some others have been said to lessen the metabolism in health, but these statements require confirmation. As regards the oxidation in the tissues as measured by the exchange of gases in the lungs, the antipyretics have not been shown to have any effect in healthy animals.

The excretion of uric acid under the antipyretics has also been the subject of repeated examination, but no definite change has been found to be induced by them.

The specific effects of the antipyretics on the **Temperature**, while recognized by all, have been the subject of endless discussion, owing to the complex mechanism through which they are elicited. In the normal animal the temperature is but little altered, except by doses large enough to produce collapse, but when it is abnormally high, as in fever, the antipyretics cause a fall of greater or less extent. This fall in temperature occurs at varying intervals after the ingestion of the drug, but, except in refractory cases, always begins within 2–3 hours. Its extent varies, the temperature sometimes reaching the normal or even a subnormal point, while in others the change is insignificant. Continuous fever without any natural rise and fall is much less affected, as a general rule, than one with alternate rise and fall of the temperature, and in the latter form the result is much greater if the drug be given at the beginning of one of the natural remissions.

The fall in temperature is often accompanied by flushing of the skin and perspiration. The oxygen absorbed and the carbonic acid excreted are lessened, and the urea and nitrogen of the urine are also diminished after antipyrine, while they are not infrequently increased after antifebrine, especially when administered in large quantities.[1] The heart is often reduced in rate, and the pulse improves in strength, but these changes are due to the fall in the temperature and not to the direct action of the drugs. Some remedies owe their antipyretic properties to their increasing the secretion of the sweat glands, but although perspiration not infrequently occurs during the fall of temperature under the new antipyretics, this is merely a secondary result here, for when the perspiration is checked by atropine or agaricin, the fall of temperature proceeds uninterruptedly.

The temperature in healthy warm-blooded animals is kept uniform through a balance being established between the heat formation and its dissipation through the lungs, skin and other organs. If an excessive formation occurs, as during muscular exertion, this is counterbalanced by an increase in the output from the skin through the dilatation of the vessels and by the perspiration. If, on the other hand, more heat is dissipated than usual through exposure to cold, the combustion of the tissues is increased and more heat is formed. The output of heat is thus determined by the degree of dilatation of the cutaneous vessels and the activity of the sweat glands, while the amount of heat formed varies with the voluntary and involuntary contractions of the muscles. In order to preserve a balance between these two factors, there must exist a coördinating mechanism, and this is supposed to be located in the basal ganglia of the cerebrum, in the region of the corpus striatum. Lesions in this neighborhood generally cause a very marked rise in the temperature, often without further disturbance, and it is of interest to learn that as long as the cerebrum is intact, shivering is produced by cold, while after the section of the peduncles the animal offers no resistance to a fall of temperature produced by cooling of the surface.

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[1] Even when the nitrogenous metabolism is reduced by antipyretics in fever, it is said to be remarkably increased as the temperature rises again, so that no real economy of proteins results from their use.

Other facts might also be adduced to show that in the normal animal the temperature is kept uniform by this coördinating mechanism, which controls both the output of heat through the skin and its formation by the contractions of the skeletal muscles. In many individuals this coördination is not perfect in health, and in all it may be disorganized by poisons, such as those formed in fever. The more perfect the coördination, the smaller is the divergence from the normal temperature necessary to elicit a protective increase in the combustion or in the dissipation. The efficiency of the mechanism may therefore be measured by observing what fall of the body temperature occurs before shivering sets in, what rise produces dilatation of the cutaneous vessels and perspiration. In this way it has been found that during fever the coördination is quite as perfect as in health, but that the protective reactions are induced at a higher temperature. Thus, Richter found that a normal dog (temperature 38.6° C.) protected itself by shivering when its temperature was reduced by cold to 37.9°, while profuse perspiration broke out when its temperature was raised to 39.1°. The same dog suffering from fever (temperature 40.4° C.) reacted by shivering when its temperature was reduced to 40.2° and by perspiration when it rose to 40.9°. The coördination is not destroyed or paralyzed by fever therefore, for it is in this case more sensitive to alterations of the body temperature than in the normal animal. The same measures are taken to preserve a uniform temperature as in health, but the temperature maintained by these means is higher. If a comparison be made with the thermostat of the laboratory, it may be said that in fever the mechanism is "set" for a higher temperature than in normal life, but that the apparatus acts efficiently for each temperature. This higher temperature is maintained by an increased metabolism or heat formation, and also in most cases by a lessened dissipation. The fever temperature itself seems to increase the metabolism, the tissues undergoing more rapid waste under it than in normal conditions.[1]

The first explanation of the antipyretic action of this series was that they lessened the metabolism in the same way as quinine, and thus lessened the heat production. This view was suggested by the fact that some of them, such as kairine and thalline, are derivatives of quinoline, like quinine, and it was supported by the observation that the nitrogen eliminated and the oxygen absorbed were reduced in amount by their action in fever. This explanation has of late years been abandoned by the great majority of the investigators of the subject. The lessened tissue waste which is observed under the action of the antipyretics in fever is not due to their direct action on the tissues, but to the fall of temperature, the metabolism proceeding more slowly when the heat is reduced. If they acted on the tissues directly in fever, they would have a similar effect in health (cf. quinine), whereas antipyrine has no appreciable effect here, and antifebrine actually increases tissue waste.

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[1] It must not be supposed from the foregoing statements that fever consists only in an alteration of the normal temperature. This is only one of the symptoms produced by the poisons of fever, but is the only one affected by the antipyretics.

Calorimetric investigations have shown that the dissipation of heat in fever is much increased by the antipyretics, while in health they seem to have little effect. This augmentation in the output is due to dilatation of the cutaneous vessels, which exposes a large amount of blood to the cold air. The dilatation is great enough to be recorded by the plethysmograph in many cases, while in others flushing of the skin may be observed. The increased dissipation of heat is accompanied by a lessened formation which, however, is much less important and which is generally attributed to the metabolism proceeding less actively at the lower temperature. In other words, the antipyretics reduce the temperature by increasing the output of heat, and the cells of the body grow and change less when removed from the hot-house temperature to which they have been exposed previously. It must be added, however, that some observers hold that the fall in heat formation is too great to be explained in this way, and suppose that the antipyretics lessen the combustion through some other action, but not by affecting the tissues directly.

FIG. 56.

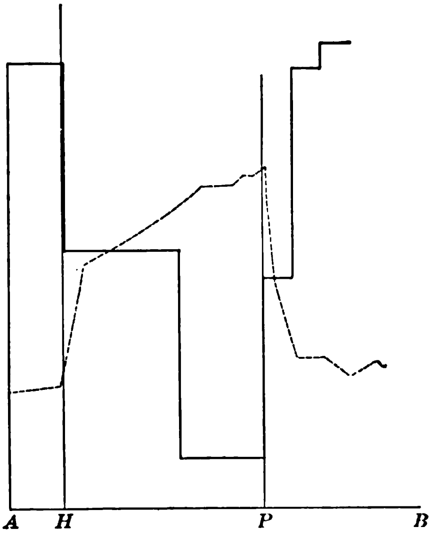


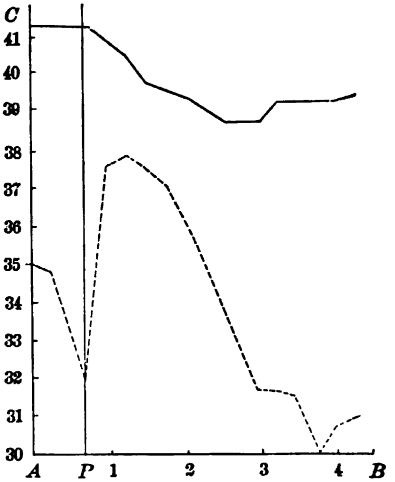
Diagram to illustrate the relation between the warmth output and the internal temperature. The unbroken line represents the changes in the warmth output, which is estimated at different times by measuring the height of this line from the abscissa *AB*. The broken line is that of the internal temperature. *A* to *H* normal; at *H* an injury of the brain caused a marked fall in the output and an increase in the internal temperature, which persisted until at *P*, antipyrine was administered. The internal temperature then fell rapidly while the output rose to beyond the normal. Contrast Fig. 54. (After one of Gottlieb's experiments.)

It has been stated already that the fevered animal resists any change in its temperature in the same way as the normal, and it might therefore be expected that when the temperature is reduced by antipyretics the organism would at once increase its heat formation. The fact that this does not occur, but that, on the contrary, the metabolism is lessened, indicates that some further change occurs, that the antipyretics not only reduce the temperature by allowing the heat to escape, but also alter the condition of the coördinating mechanism by which the temperature is kept uniform. To return to the comparison with a thermostat, the body temperature is set at a lower point by the antipyretics, while it is set higher by the fever poisons.

The action of the antipyretics on this coördinating centre is therefore of interest, and has been examined both in health and disease.

In healthy men the temperature does not undergo any marked change under the antipyretics, for though it may fall a few tenths of a degree in some cases, this is of no significance. The sensitiveness of the coördinating centre is increased apparently, however, for in some individuals in whom hard muscular work causes a rise of temperature normally, this is absent or less marked after the antipyretics. In the same way the rise of temperature which occasionally is caused by very hot baths, is absent or diminished when antipyrine has been administered previously. When the basal ganglia are cut off from their connections with the lower part of the body, neither septic injections nor antipyretics have any effect on the temperature, while after section above the basal ganglia, fever is caused, and the antipyretics induce the usual fall of temperature (Sawadowsky). In experiments in which a high fever was produced by lesions in the neighborhood of the ganglia, Gottlieb found that the antipyretics reduced the temperature and increased the output of heat to a marked extent, while the formation was increased to a less degree.

FIG. 57.



Curve of the internal temperature (unbroken line) and of the skin temperature (dotted line) in fever treated with antipyrine (Rosenthal). The abscissa *AB* represents the time in hours, the vertical, *AC*, the temperature Centigrade. At *P* antipyrine was given, and the skin temperature rose at once (augmented heat output). The internal temperature soon began to fall, and after it had reached a certain point, the skin temperature fell again as the capillaries contracted.

Finally, the condition of the centre has been examined by Stern and Richter after the temperature had been reduced by antipyretics. They both found that the protective mechanism was called into play when the temperature was slightly raised, and generally when it was depressed. For example, a fevered dog (temperature 40.9° C.) received a dose of kairine, and its temperature was reduced to 37.6°. Attempts were now made to raise the temperature by external heat, but the animal resisted this by increasing the output as soon as the temperature rose to 37.8°. The coördination which maintained the temperature at 40.9° before the drug was administered now attempted to keep it at 37.6°.

The results of these researches may be summed up shortly as follows: The antipyretics reduce the temperature in fever through alterations effected in the heat-regulating nervous mechanism, which result in lowering the point at which the temperature is maintained. As a consequence of this action, a great increase in the dissipation of heat must occur in order to free the body from the warmth which it has accumulated, and this increased output is attained by dilatation of the cutaneous vessels. The seat of action of the antipyretics is probably situated in the base of the cerebrum.

The precise nature of the changes wrought by the antipyretics in the coördinating mechanism is unknown. Gottlieb and Harnack suggest that it is depressed by them and this would accord with the widely held idea that fever temperature is due to some form of brain irritation; but their reasoning is open to objection, and speculation seems useless until more is learned regarding the normal function of this organ.

When the temperature is depressed too rapidly by these remedies, a condition of collapse is often produced, while in other cases the loss of heat caused by the dilatation of the skin vessels seems to be excessive, and shivering and rigor follow in order to increase the production.

When the temperature has reached the new point fixed by the coördination under the influence of the antipyretics, the heat dissipation rapidly diminishes and may become less than normal, because the new temperature is maintained at a constant point by the same mechanism as the normal.

The antipyretics are rapidly absorbed, and as rapidly **Excreted** by the kidneys, so that they disappear from the body within 24–30 hours after their administration.

The fate of antipyrine seems to differ in different animals. In the dog it is found to be partially oxidized to oxyantipyrine which is excreted in the urine in combination with glycuronic and sulphuric acids. In others it is said to be excreted in the urine unchanged. Antifebrine undergoes a partial oxidation, the final product differing in different animals, but none of the original body appears in the urine except after very large doses. In man it appears as acetylparamidophenol $\left(C_6H_4<\begin{matrix}NHC_2H_3O\\OH\end{matrix}\right)$ and as paramidophenol or another of its compounds, both being in combination with sulphuric and glycuronic acids. In the rabbit's urine paramidophenol alone is found, while in the dog this is accompanied by oxycarbanil $(C_2H_4<\begin{matrix}NH\\O\end{matrix}>CO)$; in each case it forms a double sulphate or glycuronate. The fate of the other antipyretics resembles that of antifebrine, the quinoline derivatives undergoing a partial oxidation resulting in a body analogous to paramidophenol, while the phenetidine compounds are partially decomposed and appear in the urine as glycuronates of phenetidine. The combinations containing salicylic acid break up in the body, and the acid appears in the urine as salicyluric acid, while the rest of the molecule undergoes the usual partial oxidation.

The presence in the urine of these bodies, or rather of further products of their oxidation, gives it a dark reddish-brown color, which may be observed when it is passed, or more frequently after it has been exposed to the air for some time.

PREPARATIONS.

ACETANILIDUM (U. S. P., B. P.), acetanilide or antifebrine.

Acetanilide is a colorless, crystalline body insoluble in water, soluble in alcohol, ether and chloroform. It has no odor when pure, but has a slight burning taste. It may be prescribed in powder, suspended in mucilage, or in cachets or lozenges. Dose 0.06–0.3 G. (1–5 grs.).

Pulvis Acetanilidi Compositus (U. S. P.) contains 7 parts of antifebrine, 1 of caffeine, and 2 of sodium bicarbonate. Dose, 0.5 G. (7½ grs.).

ANTIPYRINA (U. S. P.), PHENAZONUM (B. P.) phenazone, or ANTIPYRINE, forms colorless inodorous crystals, with a bitter taste, very soluble in water, alcohol and chloroform. 0.3–0.6 G. (5–10 grs.).

PHENACETINUM (B. P.), ACETPHENETIDINUM (U. S. P.), colorless, tasteless crystals, insoluble in water, 0.3–1 G. (5–15 grs.), in the same forms as acetanilide.

Nonofficial.

Thalline is generally seen as thalline sulphate, a colorless crystalline substance, of a weak aromatic odor and slightly bitter taste, soluble in 7 parts of water. 0.2–0.5 G. (3–8 grs.).

Exalgine resembles acetanilide except in its greater solubility in water, and may be given in the same quantity.

Malakine, Lactophenine, Thermodine, Neurodine, Saliphen and *Salophen* all resemble each other in being insoluble in water, colorless and crystalline, and are prescribed in the same way as acetanilide and in doses of 0.5–1 G.

Phenocoll is generally used as the hydrochlorate, which is fairly soluble in water, while *Salocoll* is insoluble. 0.5–1 G. (8–15 grs.).

Malakine, Saliphen, Salocoll and *Salophen* all break up in the body, freeing salicylic acid, so that, in addition to the antipyretic action, the characteristic effects of this acid may be elicited by them.

The antipyretics are almost invariably given by the mouth. Antipyrine has been injected hypodermically, but this is somewhat painful, because much larger quantities have to be used than are generally given by this method, and the solutions have, therefore, to be more concentrated (30–50 per cent.).

Therapeutic Uses.—The antipyretics are used chiefly to **Reduce the Fever Temperature.** The most satisfactory results are obtained from those which act somewhat slowly, but which preserve a low temperature for some time, and antipyretics and the phenetidine compounds are thus preferable to the earlier remedies, which produce a more abrupt fall, after which the temperature soon regains its former height. The best effects are obtained when the antipyretic is given at the commencement of a natural remission, the temperature often falling 2–4 degrees in the course of the next 2–3 hours, and only rising slowly afterwards. In some fevers the antipyretics have much less tendency to lower the temperature than in others. Thus in septicæmia larger doses are required than in typhoid and not infrequently no satisfactory reduction of the temperature follows the administration of the maximal quantity. Pneumonia is also said by some writers not to be affected so easily as some other febrile conditions in which the heat-regulating centre appears to be in a less stable condition, as is manifested by the occurrence of large spontaneous variations of temperature. The reduction of the temperature by the antipyretics lasts only as long as the drug is present in sufficient quantity in the body, and accordingly as soon as sufficient has been excreted, the intoxication of the regulating mechanism begins again, and the temperature soon rises to its former height. The antipyretics do not act on the cause of the disease, but only remove one of the symptoms, but this in itself is not an argument against their use, as is apparently believed by some writers, because as long as the physician is unable to treat the cause directly, he is justified in taking such measures as are possible to remove the symptoms, rather than in adopting an expectant treatment, pure and simple. The extensive use of these remedies shows very clearly that the high temperature is merely a symptom of disease, and not the disease itself, and the question has been much debated whether the reduction of fever is in any way beneficial. No one questions that some antipyretic measures should be taken when the temperature rises so high as to form a danger in itself, but their use in ordinary fever cases is more doubtful, and many physicians deprecate it unless in exceptional conditions. The very large doses formerly used undoubtedly induced dangerous symptoms occasionally, but there is little risk of this occurring from the intelligent use of the less violent members of the series. It has recently been shown by Schutze and Beniasch that the use of the antipyretics does not retard the formation of the protective substances (antitoxins) to which the recovery from fever is attributed, for in infected animals treated with enormous quantities of antipyrine the serum displayed the same agglutinating properties towards the bacilli as that of controls which were not subjected to any medication. A more serious argument against their use in fever is that the course of the disease is less readily followed, because one of the guiding symptoms — the temperature variations — is no longer dependent solely upon the severity of the intoxication with the fever poisons, and both diagnosis and prognosis are thus rendered more difficult. For example, in typhoid fever a sudden fall of temperature often gives the first indication of such a complication as hæmorrhage, but if an antipyretic has been given beforehand, this indication may be entirely absent. On the other hand, it is urged in favor of the antipyretic treatment that the patient feels more comfortable and easier when the temperature is reduced, and that this alone may favorably influence the course of the disease. Besides, the high temperature in itself increases the tissue waste and causes larger draughts on the resources of the patient than would be made with the same amount of poison in the tissues at a lower temperature; and although the influence of the high temperature on the metabolism was undoubtedly exaggerated at one time, this consideration is by no means devoid of weight. The theory that fever is a defensive measure taken by the organism against the causes of disease and ought not to be interfered with therefore, is now seldom mentioned. The antipyretic treatment of fever is of value, then, in cases where the temperature is so high as to endanger life, in cases in which the rise of temperature is the chief cause of distress and no complications are to be apprehended, and, in general, in cases in which the increased comfort of the patient is not counterbalanced by their obscuring the diagnosis and prognosis. On the other hand, there is no reason to suppose that it lessens the mortality or shortens the course of most fevers, or that it prevents complications of any kind except excessively high temperature, and the routine treatment of fever with antipyretics is to be deprecated.

The chief rival of the antipyretics in the treatment of fever in the present day is the so-called cold-bath treatment, in which the fever patient is bathed frequently in water the temperature of which varies from 70–90° F. in different hospitals. The temperature generally falls to a considerable extent under this treatment, and very often a general improvement in the symptoms occurs. The effect on the temperature is mainly due to the abstraction of heat from the body, and thus far corresponds to that of the antipyretics. In the cold-bath treatment, however, the loss of heat is not immediately due to the dilatation of the skin vessels, for baths at 70° F. have rather the effect of constricting the vessels primarily, whatever may be the subsequent effect. The heat output increases here from the change in the external medium, and not from any alteration in the skin itself. The fall of temperature is generally not so great as under the antipyretics, and the regulation is not directly affected, for the patient shivers and becomes cyanotic long before the normal temperature is reached. The therapeutic virtue of the cold bath was formerly believed to lie exclusively in the abstraction of heat and the fall of temperature, but many advocates of the treatment now hold that this is of less importance than the effects on the circulation and the brain, which are elicited reflexly by the cold water applied to the skin, and which are not now believed to be due to the fall in temperature. Whether this view is correct or not, the whole nature of the fall in temperature is different from that produced by the antipyretics, and the metabolism, instead of becoming less active as it does under the latter, rather tends to increase under the cold baths, at least as far as the tissue change can be measured by the nitrogen excreted. The relative therapeutic value of the two methods of treating fevers can only be determined by clinical experiment, and the present attitude of the clinicians, which tends to favor the cold-bath treatment, may be reversed in course of time. However the matter may stand in hospital practice, in which trained assistance is available, the antipyretics have a great advantage in many cases in which treatment has to be carried out without any such facilities, for the administration of these drugs may, of course, be entrusted to ordinary persons, whereas the cold bath can be given only by the physician himself or by trained attendants. Particularly in the milder fevers, where no complicated measures, such as the cold bath, are considered necessary, the antipyretics give relief to the patient by removing the feeling of heat and discomfort.

Other antipyretic drugs are quinine, aconite, digitalis and alcohol, but none of these produce an equal fall of temperature unless with the presence of alarming and dangerous symptoms. Aconite and digitalis are generally supposed to reduce the temperature through their effects on the circulation, although it is not impossible that they may also affect the centres for heat regulation. Quinine acts probably through reducing the metabolism, and alcohol by dilating the skin capillaries, and perhaps by lessening the movements and thereby the formation of heat. All of these drugs are used very much less as antipyretics now than formerly, as, besides their undesirable secondary effects, the fall of temperature is less certain and less profound than under the modern antipyretics.

The antipyretics are also used very largely to relieve **Neuralgic Pain and Headache,** often with complete success. The analgesic action of these bodies is apparently quite different from that of morphine, for in many instances in which the latter is successful they fail to alleviate the condition. On the other hand antipyrine and its allies can often be used where morphine is contra-indicated, either from the danger of the habit being formed, or from the somnolence it induces. The antipyretics appear to be of little or no value in relieving the pain caused by acute inflammatory conditions, while on the other hand they are almost specific in some neuralgic cases. Almost all of the antipyretics are efficient in these cases, but larger doses are generally required than to reduce fever, and the more powerful, such as antifebrine, are often preferred to the safer and more slowly acting phenetidines. Caffeine is often prescribed along with the antipyretic, as in the compound acetanilide powder.

Several of the antipyretics have been used as **Substitutes for Quinine** in the treatment of malaria, but none of them seem to have the specific action of the latter on the organism of malaria, and, although they may reduce the temperature, they do not prevent the other symptoms and do not remove the cause of the disease. In the same way they do not seem to equal salicylic acid in efficiency in acute rheumatism, although here again they reduce the temperature. This does not apply, of course, to those of the antipyretics, such as malakine, which from salicylic acid in their decomposition in the body. It is to be noted that the amount of salicylic acid thus formed from the ordinary dose of the antipyretics, is considerably smaller than would be given if the acid itself were prescribed.

The antipyretics are used to a considerable extent in cases of diabetes insipidus and mellitus and appear to relieve the discomfort and in some cases to improve the general condition. In whooping cough antipyrine often lessens the severity of the attacks and also renders them less frequent, and is said to shorten the course of the disease.

The use of antipyrine and other members of this series as sedatives in hyperactivity of the motor functions of the brain, such as epilepsy and chorea, has not been attended with great success, although temporary improvement has occasionally been noted, as after so many other remedies.

Antipyrine and several others of this series have been advocated as local sedatives or anæsthetics, and have been used occasionally to lessen the irritability of the throat and larynx and thus to permit of the minor manipulations of laryngology. Holocaine, a body closely related to phenacetine, has been employed to a limited extent as a local anæsthetic in ophthalmology, but appears to be more poisonous than other equally efficacious drugs, such as eucaine.

Thalline has been advised as a urethral injection in gonorrhœa.

The occurrence of collapse and other symptoms has led to a considerable amount of distrust of the antipyretics among many of the medical profession. In justice it has to be remembered that in many cases these symptoms were produced only by very large doses, and that since experience has shown that beneficial results may be obtained by smaller quantities, these cases have notably diminished in medical practice. Unfortunately, this distrust is not entertained by a large class of the laity, and numerous cases of poisoning arise from the impression that the antipyretics are not dangerous drugs. For the most part, poisoning seems to be due to a peculiar sensitiveness or idiosyncrasy, which cannot be foreseen, but in cases of great exhaustion and asthenia, especially when accompanied with anæmia, these drugs have to be used with great care or avoided entirely.

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XXIX. ANTISEPTICS OF THE AROMATIC SERIES (CARBOLIC AND SALICYLIC ACID SERIES).

Various balsams and wood-tar and some of its derivatives have long enjoyed a certain reputation in surgery, but the true value of the bodies of the aromatic series has only been realized since the systematic treatment of wounds with antiseptics was introduced by Lister some forty years ago. The first antiseptic proposed by him was carbolic acid, and this held its position for several years, when it was discovered that bodies of similar origin, and others of entirely different composition possessed equally great advantages as antiseptics with less liability to induce poisoning. Of late years a very large number of antiseptics belonging to the aromatic chemical series have been introduced, and have been discarded, often, it would appear, without sufficient examination. It is not within the scope of such a work as this to examine all of these, especially as the effects of many of them differ only in detail, but the chief active principles will be mentioned.

The great mass of the aromatic antiseptics are obtained from coal- or wood-tar by more or less complicated reactions and are often known as the coal-tar or tar antiseptics.

The hydrocarbons *benzene or benzol, toluol, xylol* are too volatile for use as antiseptics, and the only hydrocarbon used for this purpose is **Naphtalin** ($C_{10}H_8$).

Among the hydroxyl compounds of benzol, **Carbolic Acid** or phenol (C_6H_5OH) is the best known. The dioxybenzols ($C_6H_4(OH)_2$), three in number, *hydroquinone, pyrocatechin* and *resorcin,* have also been used in medicine, and resorcin was at one time a popular antiseptic, although it has latterly fallen into disuse.

Among the trioxybenzols, **Pyrogallol** ($C_6H_3(OH)_3$) alone has been used extensively as an antiseptic in skin diseases, and is still considered of value in certain conditions.

Hydroxyl derivatives of other hydrocarbons are the two **Naphtols,** α- and β-, ($C_{10}H_7OH$), sometimes used as intestinal disinfectants. *Thymol* ($C_6H_3(CH_3)(C_3H_7)OH$), obtained from thyme, was introduced as a substitute for carbolic acid, but has fallen into disuse. More recently the *cresols,* $C_6H_4(OH)(CH_3)$, of which three are known, have attained some prominence as antiseptics.

The phenol ethers, *anisol* and *phenetol* ($C_6H_5OCH_3$ and $C_6H_5OC_2H_5$) have never been introduced into therapeutic use, but *guaiacol* ($C_6H_4(OH)(OCH_3)$), the methyl ether of pyrocatechin, has had some use of late years as an antiseptic and antipyretic. A combination of guaiacol and carbonic acid known as *guaiacol carbonate* ($CO(OC_6H_4OCH_3)_2$) has also been used. Other dioxy-derivatives are the *creosols* ($C_6H_3(CH_3)(OH)(OCH_3)$), which are important constituents of wood-tar and of creosote.

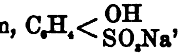
The substitution of chlorine for hydrogen in the benzol ring seems to increase its antiseptic power, and *monochlorphenol* (C_6H_4ClOH) and *trichlorphenol* ($C_6H_2Cl_3OH$) have been suggested as antiseptics. A similar intensified action is obtained by the substitution of chlorine in the members of the methane narcotics.

The presence of the carboxyl group (—COOH) lessens the poisonous action of the aromatic series exactly as in the case of the methane series. Several acids have been suggested as internal antiseptics, therefore, and one of them, **Salicylic acid** ($C_6H_4OHCOOH$), is perhaps the most important of all the benzol compounds at the present time. **Benzoic acid** (C_6H_5COOH) is an equally powerful antiseptic, but is comparatively seldom used as such. It is the chief constituent of several of the "balsams," in which it is often accompanied by *cinnamic acid* ($C_6H_5CH{=}CHCOOH$).

Salicylic acid is the only one of three isomeric acids that has been found of value. It is used either as the pure acid or more frequently as the **Salicylate of Sodium**, or in the form of an ester. One of these, *methylsalicylate*, has long been known as the *oil of wintergreen* and as *sweet oil of birch*. Another well-known ester is the phenyl salicylate or **Salol**, ($C_6H_4OHCOOC_6H_5$), while others of less widespread reputation are *cresalol* (salicylate of cresol), *betol* (salicylate of β-naphthol), *salithymol* (salicylate of thymol). Several other salicylic compounds are used as antipyretics as well as for their action as salicylates and are mentioned among the antipyrine series. (Page 425.) The most recent substitute for salicylic acid is *aspirin* or acetylsalicylic acid ($C_6H_4OC_2H_3O{\cdot}COOH$).

Another acid which has been used as a substitute for salicylic acid is *cresotinic acid* ($C_6H_3(CH_3)(OH)(COOH)$), and the *oxynaphtoic acids* ($C_{10}H_6(OH)(COOH)$) have been suggested as antiseptics.

Instead of carboxyl, the sulphon radicle has been attached to phenol in order to lessen its toxicity, and in this way the so-called *sulphocarbolates* were formed. They must be distinguished from the ether-sulphuric acids or double sulphates in which the $-HSO_3$ is attached to the carbon of the ring by oxygen, while in the sulphocarbolates the connection between the sulphur and the carbon is direct. (Sulphocarbolate of sodium,



$C_6H_4{<}\begin{smallmatrix}OH\\SO_3Na\end{smallmatrix}$, sodium-phenol double sulphate, $C_6H_5OSO_3Na$.)

When two hydrogen atoms of the benzol molecule are substituted by other elements or radicles, three different chemical products may result, and these are known as ortho-, meta- or para-compounds, according to the relation the two substituted atoms bear to each other. These three isomeric forms very often differ in toxicity and also in their antiseptic power, but no general statement can be made as to their relative position, for the ortho-compound is sometimes the most powerful antiseptic, as in salicylic acid; in others the meta-compound, as in metacresol, while parachlorphenol is more strongly antiseptic than either ortho- or metachlorphenol.

Many crude preparations of these bodies are still in use and have the advantage of cheapness over the pure principles, and are therefore preferred where disinfection has to be carried out on a large scale.

Wood-tar varies in its composition with the wood from which it is obtained. The most important constituents are generally guaiacols and creosols and their homologues, while carbolic acid and the cresols are less largely represented. Along with other only partially known substances, some hydrocarbons and acids such as acetic acid, also occur.

Creosote is obtained from beech tar and consists chiefly of guaiacol and creosols with very little carbolic acid or cresol, which latter have a lower boiling point and are removed in the course of preparation.

The *volatile* or *ethereal oils* have also antiseptic properties, and, in fact, no line of demarcation can be drawn between the volatile oil series and the antiseptics proper, for many bodies occur in both groups, and the great majority of the constituents of the volatile oil series belongs to the benzol compounds. The earliest antiseptics known were those occurring in plants, as is shown by the use of various herbs in embalming in Egypt. In later times several of the balsams, which contain benzoic and cinnamic acids dissolved in volatile oils, were credited with beneficial effects in the treatment of wounds.

Action.—The simpler bodies of the aromatic series produce symptoms in the living organism which present great similarity in their general features, although they differ in details. As a general rule it is found that the simpler members of the series are much more poisonous to the higher animals than the more complex ones, while the latter are equally or more efficient as poisons in the lowest living forms. They are all possessed of a more or less marked action on the central nervous system, which is thrown into a condition of abnormal irritability, manifested in increased reflexes, tremor and convulsions. Later, a stage of prostration and collapse is developed, which may simulate that induced by chloral and its allies, but does not seem to be identical with it, for though in man the consciousness is often lost in this stage, the collapse in animals is in many cases not accompanied by loss of sensation or of the voluntary movements. The symptoms are generally those of great muscular weakness and indicate depression of the vital centres of the medulla oblongata and of the heart rather than complete loss of the cerebral functions. They resemble surgical shock more than the anæsthesia following the use of chloroform and ether, and are probably of a different nature from the latter.

Many of the members of the benzol series tend to destroy the red cells of the blood and to form methæmoglobin; this effect is especially developed in the case of pyrogallol and will be described under it in detail. Most of these antiseptics reduce the temperature in fever, while they have little effect on that of the normal body unless when given in large enough quantities to produce collapse. The cause of the fall of temperature in fever under the action of these drugs is not satisfactorily explained, although it seems probable that the process is the same as in the antipyrine series, with which they are nearly allied.

The aromatic poisons differ from the typical members of the methane series in their effects on protoplasm in general. Alcohol and ether destroy life in all forms of protoplasm when they are brought in contact with it in sufficient concentration, but the phenols and acids of the aromatic series do so in more dilute solutions, and in fact owe their importance in medicine to their activity as general protoplasm poisons.

Small quantities of the aromatic bodies seem to increase the activity of living matter, at any rate under some conditions, for the alcoholic fermentation is said to be accelerated by the presence of minute proportions of these poisons, and in the higher animals some of them increase the nitrogenous metabolism, while larger doses destroy the yeasts and also the tissues of the body. The symptoms of central nervous irritation might also be cited in support of the view that the members of the aromatic series first accelerate and then retard protoplasmic activity, but the evidence is too limited as yet to admit of such a generalization.

Therapeutic Uses.—The members of the aromatic series are used in therapeutics chiefly as disinfectants and antiseptics, that is, to destroy or retard the growth of pathogenic and putrefactive microörganisms and yeasts. Their introduction by Lister to prevent the infection of wounded surfaces in surgery was followed by a revolution in surgical methods, which can only be paralleled by that which followed the introduction of anæsthetics some twenty years earlier.

The successful treatment of local infections by means of antiseptics encouraged the hope that general septic diseases might be as favorably influenced by them, but the two conditions are obviously entirely different, for in the case of a local infection the remedy may be applied at the diseased point, and, although it may destroy the life of the superficial cells in the neighborhood, this is not of vital importance. On the other hand, a disinfectant, acting throughout the tissues of the body in sufficient quantity to destroy the microbes of infection, must have an equally unfavorable effect on the cells of the host, unless it has a specific action on the parasite, and this is very exceptional.

A disinfectant in the strict use of the term is a substance used to destroy microbes, while an antiseptic, while not actually killing the germs, prevents their growth as long as it remains in contact with them. A disinfectant is accordingly only intended to act for a short time, for if the infected matter be once rendered sterile it can only become dangerous by being again contaminated. For example, a room requires only to be disinfected after a case of infectious disease. A wound, on the other hand, even though completely disinfected may become contaminated again very easily and an antiseptic may be required to prevent the further growth of microbes. Many substances are disinfectant in large quantities and antiseptic in more dilute solutions, but others are too weak to disinfect thoroughly though they retard the growth of pathogenic organisms, and still others may be employed to disinfect but are unsuitable for use as antiseptics, either because they are too poisonous to be applied for a sufficient time, or because they lose their effects on the microbes (peroxide of hydrogen group).

The uses of the antiseptics and disinfectants may be stated as follows:

1. **To Disinfect Rooms, Furniture, Clothes,** etc.—For these purposes the strongest and cheapest drugs which do not actually injure the objects may be employed. None of the aromatic series is very trustworthy here, although carbolic solution has been employed; the gaseous disinfectants, formaldehyde and sulphurous acid, are much more efficient. For the disinfection of the excrementa, crude carbolic acid and tar have been advocated.

2. **To Prevent the Infection of Wounds** in surgery. This was first attained by Lister's carbolic acid dressing and operative procedure, but many other antiseptics have since been substituted for carbolic acid, and the use of antiseptics during operations on uninfected organs has given way to the aseptic method. For use during operations on infected wounds, the disinfectant must be soluble or miscible in water, and ought to produce as little irritation as possible, but there is less likelihood of serious poisoning or irritation from the use of antiseptics here than from their subsequent application to the wounded surface as dressings. The importance of avoiding the use of irritant antiseptics in operations on delicate structures, such as the peritoneum, has only been fully recognized of late years. Where a dressing has to be

applied for some time, and especially when the wounded surface is large, as in the case of burns or large abscesses, the danger of absorption has to be taken into consideration and antiseptics ought therefore to be chosen which are either absorbed slowly or are not very poisonous to man. The frequent occurrence of more or less severe carbolic intoxication has led to its employment being much more restricted than formerly, while the less soluble or less poisonous antiseptics have taken its place.

3. **In the Treatment of Skin Diseases** the danger of absorption is even greater than in the dressing of wounds, as the absorbing surface is often very much more extensive, and in addition the more irritant antiseptics are obviously not admissible here. In many cases of successful treatment with bodies of the aromatic series, the remedy seems to act not only as an antiseptic but also as a mild irritant and astringent. Pyrogallol is believed by some dermatologists to be of value only from its reducing action depriving the superficial tissues of their oxygen.

4. The antiseptics have been frequently employed for their **Disinfectant Action on the Bowel,** and as far as the putrefaction of the intestinal contents is concerned, with some success. Too high value has often been assigned to this method of treatment, owing to the erroneous ideas that the disintegration of the food by microbes could be estimated by the amount of double sulphates or indol in the urine, and that the number of microbes in the fæces afforded an index of the intestinal putrefaction; but after discounting this, there remains sufficient evidence that the infection of the intestinal contents can be reduced by the use of antiseptics. It is now generally conceded, however, that intestinal putrefaction is more satisfactorily treated by evacuation of the contents by a purgative such as one of the mercurial preparations, which also have a high disinfectant value. When bacterial infection of the wall of the bowel is treated with these antiseptics, the results are still less favorable. In typhoid fever, in which the subject has been most frequently examined, the number of the typhoid bacilli in the stools has not been lessened to any noticeable extent, and the use of these drugs does not relieve the symptoms or shorten the duration of the disease.

Any drug used for the disinfection of the intestine must not be irritant, nor very poisonous. It must not be too soluble, since otherwise it may be absorbed from the upper part of the bowel, and on the other hand it must be soluble to some extent, or it cannot mix very intimately with the contents of the intestine. Carbolic acid is scarcely fitted for this purpose, for it irritates the stomach and is also rapidly absorbed. Some of the cresols have been recommended of late years, and the naphthalin preparations have also enjoyed some reputation. Salol and its congeners have the advantage of being almost completely insoluble and harmless in the stomach and of being dissolved and rendered active by the intestinal juices, and have been found of value in excessive putrefaction of the contents of the bowel.

5. The antiseptics of the benzol series are excreted in great part by the kidneys, and the urine is thus rendered weakly antiseptic and irritant. This fact has been taken advantage of in the treatment of **Septic Diseases of the Bladder and Urethra**; the drugs used for this purpose must not be too irritant to the gastric mucous membranes, and must be easily absorbed, and not dangerously poisonous. Here, again, salol has been found of value as well as salicylic acid. The forms in which the benzol derivatives are excreted by the kidney are generally much less irritant and antiseptic than those in which they are administered. In estimating the value of each as a urinary disinfectant, it must also be remembered that many of them are liable to undergo oxidation in the urine itself. (See also copaiba series and urotropin.)

Attempts to render the bile antiseptic by means of drugs excreted by the liver have not hitherto proved successful, though some of the benzol antiseptics, such as thymol, are found in it when given by the mouth.

6. Small quantities of some of the more volatile members of this series, especially of the hydrocarbons, escape by the lungs, and this has led to their use in **Pulmonary Disease**, especially in phthisis. It may be stated at once that careful observers are united in the belief that the internal administration of these remedies has practically no antiseptic effect on the microbes in the lungs. Some relief is often obtained, but, it is believed, only through their disinfectant action in the stomach and bowel. Antiseptic remedies have also been inhaled in vapor or spray and have been injected into the trachea and even into the lung directly, but as far as the tubercle bacillus is concerned, they have had no result in the hands of the vast majority of physicians. In cases of gangrene of the lung, fœtid bronchitis, etc., the inhalations relieve the patient to some extent, and certainly lessen the offensive odor.

7. The use of antiseptics to **Destroy Pathogenic Germs in the Tissues after Absorption** is very limited. It is now recognized to be hopeless to attempt to find a single body which will destroy all forms of bacteria in the tissues, while leaving the host uninjured, but there is still reason to believe that in the future specific antiseptics may be found for at least some of the constitutional diseases. Such a specific action is seen in the effects of quinine on the organism of malaria, of salicylic acid in rheumatic fever, of mercury in syphilis and of arsenic and antimony in various trypanosome infections,[1] all of these apparently acting more strongly on the cause of the disease than on the tissues of the patient. While it may be hoped that the antiseptic treatment of internal maladies has not reached its final limit, the only constitutional disease in which the aromatic series has been shown to be of

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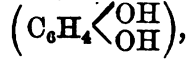
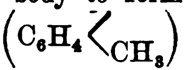
[1] It is to be remarked that in malaria, syphilis and trypanosomiasis, in which specifics have been obtained, the disease is due to invasion by protozoa, while most of the infections of which the cause is known, arise from bacteria, and these appear to be much less susceptible to the action of chemical agents.

incontestable value is acute rheumatism, and in many other conditions which were formerly treated with benzol antiseptics they have proved rather injurious than otherwise. It is futile, then, to attempt to disinfect the tissues generally with ordinary agents, which are much too poisonous. And it has recently been shown by Bechhold that many substances which are powerful disinfectants in ordinary fluids lose their activity in protein solutions, owing to their forming combinations with the proteins, so that though they are not dangerous to the host, they are comparatively innocuous to the microbes in the tissues. For example, a disinfectant which prevented the growth of diphtheria germs in broth when added in the proportion of one in half a million had no action on the germs in the tissues when it was present in the proportion of one in five thousand, because it combined with the tissue proteins in preference to those of the bacilli.

There is reason to believe that solutions containing several of the benzol series are more strongly antiseptic than those containing an equal percentage of the individual pure bodies, and that the mixture of such a body as carbolic acid with an antiseptic of another kind, *e. g.,* mercuric perchloride, is still more efficient than the corresponding proportion of either alone. This appears to be due to a change in the solubility of the disinfectant, at any rate in some cases.

If a poison is to penetrate into the interior of an organism in quantity, it must be as soluble in the protoplasm as in the fluid in which it is applied, for it is obvious that it will not leave a medium in which it is readily soluble for one in which it is dissolved with difficulty. Accordingly, it is found that fats and oils in which the members of the aromatic series are very soluble are not suitable as media for their application, for the poisons remain in the oily menstruum and fail to penetrate the microbes in which they are less soluble. On the other hand, the addition of inorganic salts to an aqueous solution of carbolic acid often increases its antiseptic power, because the poison becomes less soluble in the water and shows a greater tendency to escape from it into the interior of the microbes.

Fate in the Tissues.—The fate of the members of the aromatic series in the body is very uniform in one respect—the benzol ring is ruptured only with great difficulty. In the great majority of cases the changes which these substances undergo in the tissues affect only the hydrogen or the side chains attached to the carbon atoms, and leave the form in which these last are attached to each other unchanged. The chief exceptions to this rule are pyrogallol and gallic acid, which seem to undergo more or less complete oxidation to carbonic acid and water. Some oxidation takes place in the aromatic series, however, the simpler forms, such as benzol and aniline, tending to form hydroxyl compounds, while those with a side chain formed of methane derivatives tend to oxidize it to carboxyl. The oxidation of the benzol compounds in the tissues therefore results in the formation of oxybenzols and aromatic acids, and this oxidation is probably not limited to any one particular tissue or organ. These bodies are not, however, excreted in this form in ordinary cases, but enter into secondary combinations in which they appear in the urine. The hydroxyl bodies unite with sulphuric and glycuronic acids to form double sulphates (ether-sulphuric acid salts) and glycuronates, while the aromatic acids are excreted in combinations with glycocoll, which are known as hippuric, salicyluric, etc., acids. The last synthesis probably occurs chiefly in the kidney, while the double sulphates are said to be formed in the liver.

A few examples of the changes undergone in the tissues may elucidate the above statement. Benzol (C_6H_6) is oxidized to phenol (C_6H_5OH), and to dioxybenzols  $\left(C_6H_4{<}\begin{array}{l}OH\\OH\end{array}\right)$, which combine in the kidney with sulphuric and glycuronic acids to form phenol-sulphuric ($C_6H_5O—SO_3H$) and phenol-glycuronic acids, and the corresponding dioxybenzol compounds. Toluol ($C_6H_5—CH_3$) is oxidized to benzoic acid ($C_6H_5—COOH$), which combines with the glycocoll of the body to form hippuric acid ($C_6H_5CO—NHCH_2COOH$). Xylol  $\left(C_6H_4{<}_{CH_3}\right)$ is oxidized only in one side chain and forms toluic acid $\left(C_6H_4{<}\begin{array}{l}CH_3\\COOH\end{array}\right)$, which is excreted in combination with glycocoll as toluric acid.

Although a general resemblance exists in the oxidation products of these bodies in the tissues and in the forms in which they are excreted, considerable differences are noted in the details. Thus, naphtalin undergoes the same oxidation as benzol, forming naphtol in place of phenol, but while the phenol appears in the urine in combination with sulphuric acid almost entirely, the naphtol combines with glycuronic acid for the most part.

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1. Carbolic Acid.

Carbolic acid, or phenol, the first of the modern antiseptics to be introduced, acts like the rest of the simpler benzol compounds as a **General Protoplasm Poison,** although in the vertebrates it acts more powerfully on the central nervous system than on the other tissues.

Its poisonous effects are well seen when it is applied to unicellular organisms, such as the *protozoa.* Even dilute solutions cause immediate arrest of all movements; the organism assumes a spherical shape and loses its transparency, and, unless the solution be very attenuated, dies in the course of a few minutes. *Plant cells* are acted on the same way, and the individual cells of more highly organized animals, such as the *ciliated epithelium* of the air passages and the *spermatozoa,* are killed at once when brought in contact with carbolic acid. There is some evidence, however, that very dilute solutions of carbolic acid, as of other antiseptics, tend to increase the activity of protoplasm, for while solutions of phenol, such as are used as surgical antiseptics, are immediately fatal to the yeast plant, very dilute solutions increase its activity. The effect of carbolic acid on protoplasm has, however, been studied chiefly in the *bacteria.* Its antiseptic power, while always considerable, is found to vary greatly with the species of microbe. Thus, while it is fairly poisonous to the ordinary pyogenic organisms, it has to be present in very concentrated form to destroy the more resistant spores of anthrax, and like other antiseptics, is much less poisonous to the microbes than to the protozoa and other simple forms of life. The development and reproduction of many microörganisms has been found to be much delayed, or altogether prevented, as long as they remained in a solution of one part of carbolic acid in 400–600 parts water, but in order to kill the spores very much more concentrated solutions (5 per cent.) were required, and Koch found that the spores of the anthrax bacilli were destroyed by 5 per cent. carbolic solution only after they had remained in it for two days.

It seems to vary considerably in its action on the *unorganized ferments;* thus it is said not to retard appreciably the fermentations produced by emulsin, diastase and myrosin, even when present in the solution up to 5 per cent., while pepsin, ptyalin and the rennet ferment are weakened by somewhat smaller quantities.

Carbolic acid precipitates **Proteins** in solution and also in the cells. It does not seem to enter into any such firm combination with them as is formed when tannic acid or a salt of one of the heavy metals is added to a solution of protein, for it can be washed out of the precipitate with comparative ease. It results from this that carbolic acid penetrates more thoroughly than the metallic antiseptics, which are rendered insoluble by the albumin they meet, and whose action therefore tends to remain confined to the surface.

This coagulation of the proteins occurs whenever carbolic acid is brought in contact with the tissues. On the **Skin** a white, opaque scar is formed by concentrated phenol, which becomes red and shining afterwards and then falls off in a few days, leaving a light brown stain which may remain for several weeks. Even a five per cent. solution applied to the fingers produces tingling and warmth, which is often followed by opacity and shrinking of the epidermis and a sense of numbness. This numbness may amount to almost complete anæsthesia if more concentrated solutions are applied, no pain being felt even when the skin is cut through. When applied for some time and prevented from evaporating, carbolic acid may cause extensive dry gangrene of the part from its penetrating through the surface layer and reaching the deeper tissues. Applied to a **Wound** in five per cent. solution, phenol induces pain and irritation and the formation of a white pellicle of coagulated proteins. It causes irritation and necrosis of the **Mucous Membranes**, and if applied in sufficient quantity may lead to sloughing and acute inflammation. This local effect may prove fatal from shock and collapse when large quantities of the undiluted acid are swallowed, the effects resembling exactly those produced by other corrosive substances.

Apart from its local action, carbolic acid has important effects after its absorption into the blood. The most marked of these are the changes in the **Central Nervous System.** When a small quantity of carbolic acid is injected into the *frog,* the first symptoms, apart from those produced by the pain of the injection, consist in an unusual quiet and in the absence of the spontaneous movements. Later, quivering of individual muscles, and apparently of the individual bundles of muscle fibres, sets in, and this is soon accompanied by an increase in the reflex irritability and eventually by convulsions similar to those seen after strychnine. These movements gradually become weaker, and eventually complete paralysis is induced, while the heart continues to beat and the muscles and nerves react to the electric shock. A dilute solution of carbolic acid applied directly to the exposed spinal cord paralyzes the sensory elements immediately, while leaving unaffected the motor fibres and the cells of the anterior horn (Baglioni).

In *mammals* a very similar set of symptoms are produced, save that there is often no noticeable preliminary stage of depression. Some weakness and lethargy may be present, however, and is followed by marked muscular tremor, which resembles the shivering produced by cold. At intervals this is interrupted by sudden twitches in different muscles, and later by clonic convulsions. The respiration and the pulse are at first accelerated, but afterwards are slow, irregular and weak. The movements become feeble and appear at longer intervals, the respiration is shallow and irregular, and the animal passes into a condition of collapse, in which, however, the sensibility to pain is often preserved. Eventually death occurs from asphyxia. After very large doses the collapse may be immediate, no convulsions being observed, the heart and respiration often ceasing simultaneously. In most cases salivation is a marked symptom, and the temperature often falls far below the normal.

In *man* convulsions are comparatively rarely seen. When large quantities are taken, immediate unconsciousness may result and death follow within a few minutes. How far this is due to the local corrosion, and how far the direct action on the central nervous system is involved, cannot be determined. In more gradual poisoning, depression and weakness, headache, nausea and vomiting are followed by giddiness, noises in the ears, pallor and collapse, with irregular pulse and respiration, and cold perspiration; fainting and unconsciousness then lead to failure of the breathing and death. Delirium and excitement have been observed in some cases. Fatal poisoning may arise from swallowing the concentrated or dilute solution, or from absorption from wounds and abscesses. It has also occurred in man from absorption through the unbroken skin.

The autopsy sometimes gives no special indications of the cause of death, save the local corrosion of the alimentary canal. Inflammation and necrosis of the intestine is said to have been observed in some cases in which the poison was absorbed from skin wounds, and fatty degeneration is sometimes induced in the liver and the renal epithelium, but is not constant.

The convulsions in the frog arise from an increase in the irritability of the spinal cord, especially of the cells of the anterior horn (Baglioni), for they are not arrested by section of the medulla oblongata. In mammals the sudden contractions of isolated muscles appear due to a similar action on the spinal cord, but the clonic convulsions and the persistent tremors are probably of cerebral origin, and Berkholz found the cerebral cortex abnormally irritable after carbolic acid. The rarity of convulsions in man has not been satisfactorily explained. In some cases the course of the intoxication is too short, the large amount of poison swallowed inducing immediate collapse, while in others their absence may be due to the debility of the patient from disease; but in a considerable number of cases of poisoning in which neither of these conditions was present, no convulsions were observed. A similar contrast between the effects of a poison on the lower animals and on man has been mentioned already under morphine. In all cases the primary stimulation of the central nervous system is followed by depression and paralysis if large doses are administered.

The acceleration of the **Respiration** and of the **Heart** seen in mammals has been supposed to be an indirect result of the increased muscular movement and convulsions, but this seems to be incorrect, for the heart is found to be accelerated before the convulsive movements and tremor appear, and the frog's heart is accelerated in cases where no movements whatever occur. It would seem probable that the acceleration of the heart is due to direct action on the muscle or on the regulating nerves. The subsequent slowing is undoubtedly due to muscular action.

The acceleration of the respiration precedes the increased movement also, and would therefore seem to be due to action on the medullary centre, which is first stimulated and later paralyzed. The vasomotor centre is said by Gies to be depressed at once by the injection of carbolic acid into the blood, but it may be questioned whether it too is not first excited when the poison is absorbed more slowly. It is undoubtedly depressed in the later stages of poisoning, and this, together with the weakness and slowness of the heart, causes a fall in the blood-pressure.

The peripheral **Nerves and Muscles** do not seem to be affected in general poisoning in mammals, although in the frog their irritability and the capacity for work of the muscle may be somewhat reduced. On the direct application of solutions of carbolic acid to the nerves or muscles, these are at once killed, like other forms of living matter.

The increased **Secretion** of saliva, perspiration and tears which is seen in poisoning in mammals is probably of central origin, and may possibly be associated with the nausea and vomiting.

The fall in **Temperature** in carbolic acid poisoning seems, for the main part, to be due to the collapse, although it is impossible to state how far this may be aided by some alteration of the regulating function, such as is seen in the closely related group of the antipyretics.

Carbolic acid added to the defibrinated **Blood** leads to the slow formation of methæmoglobin, but this does not occur in the living animal. Occasionally some destruction of the red blood cells is caused in animals through the injection of carbolic acid directly into the blood vessels, and in one case of poisoning in man hæmoglobin was detected in the urine, indicating that some of the red cells of the blood had been destroyed.

Excretion.—Carbolic acid passes through the tissues unoxidized for the most part, but a certain proportion of it undergoes a partial oxidation to hydroquinone and pyrocatechin. These combine in the body with sulphuric and glycuronic acids, and are excreted in the urine as double sulphates (ether sulphates) and glycuronates of phenol, hydroquinone and pyrocatechin. The two last-named bodies are somewhat unstable and tend to undergo further oxidation, through which colored substances are formed. When carbolic acid has been absorbed, therefore, the urine tends to assume a dark, dusky-green color which may change to brown or even black. This change may occur in the body, and the urine is very often passed of a greenish-brown color, but further oxidation takes place on exposure to the air, resulting in deeper coloration which commences at the surface of the fluid and gradually extends downwards. The depth of the shade depends not on the amount of phenol sulphate in the urine, but on that of the dioxybenzols, and a darker urine is often observed, therefore, when the absorption has occurred from an open wound (in which the conditions are especially favorable to oxidation) than from much larger quantities absorbed from the alimentary canal.

The presence of glycuronates in the urine may lead to its reducing Fehling's solution, and thus give rise to the suspicion of glycosuria. On the other hand, the passage of these bodies through the kidney often causes some irritation and albuminuria. The double sulphates of the urine are, of course, much increased, and in the dog the whole of the ordinary inorganic sulphates may disappear, the urine containing only double sulphates.

The **Chlorphenols**, in which chlorine is substituted for one or more of the hydrogen atoms of carbolic acid, are much more poisonous to microörganisms than the original substance, but are also somewhat more poisonous to mammals, so that they have not been much used. A similar intensifying effect is seen in the chlorine substitution products of the narcotic series, *e. g.*, chloroform. The most poisonous of the monochlor-phenols is parachlorphenol. Bromol or tribromphenol has been used to a limited extent in therapeutics as a disinfectant and caustic.

PREPARATIONS.

ACIDUM CARBOLICUM (B. P.), PHENOL (U. S. P.), carbolic acid or phenol (C_6H_5OH) forms colorless, deliquescent crystals when recently prepared, but often assumes a reddish tinge from oxidation. It has a characteristic odor and is intensely corrosive. It is soluble in about 20 parts of water, but becomes liquid when 10 parts of water are added to 90 of the crystals, forming the *Acidum Carbolicum Liquefactum* (B. P.), *Phenol Liquefactum* (U. S. P.). This must be carefully distinguished from the ordinary solution of carbolic acid, which contains only about 5 per cent. of phenol, while the liquefied carbolic acid contains about 90 per cent.

Carbolic acid, 0.03–0.2 G. (½–3 grs.).

Liquefied carbolic acid, 1–3 mins.

Glyceritum Phenolis (U. S. P.), *Glycerinum Acidi Carbolici* (B. P.), 20 per cent. of carbolic acid in glycerin. 0.3 c.c. (5 mins.).

Unguentum Phenolis, U. S. P., 3 per cent.; *Unguentum Acidi Carbolici,* B. P., 4 per cent.

Carbolic acid is generally used in 2–5 per cent. solution. A crude, impure form may be employed to disinfect stools, latrines, etc. The ointment is comparatively seldom prescribed, as it is found more irritant than many other equally powerful antiseptics. The glycerite may be used as a very weak caustic. Solutions of carbolic acid in oil have little or no antiseptic action, because they fail to penetrate into the microbes.

Therapeutic Uses.—Carbolic acid is used as an antiseptic in surgical operations in 2–5 per cent. solution in water. It now plays a much less important rôle in surgery than it did in the first days of antisepsis; in fact in many clinics in which it was once the only antiseptic used, and in which it was applied in all the manifold preparations then known, carbolic acid is now employed only to preserve the instruments from infection. This change is no doubt partially due to apprehension of its irritant action, and to the occasional cases of poisoning which occurred from its use, but chiefly to the alterations in surgical technique which have been introduced since the antiseptic method was first invented. The tendency now is to reduce the use of antiseptics to a minimum and to trust instead to stricter cleanliness and asepsis. Its irritant action and the danger of absorption have also rendered it unpopular as a dressing or lotion after operations or injuries, where there is any large absorbent surface, or where irritation is liable to be injurious, as in most forms of skin disease.

It is still used as a disinfectant in septic wounds, though greater reliance is now placed on corrosive sublimate and the oxidizing germicides, such as hydrogen peroxide. Strong carbolic acid has been applied to disinfect wounds, its poisonous effects being avoided by immediately washing it off with alcohol.

Harrington has recently drawn attention to the danger of applying dilute solutions in bandages to injured fingers and hands; he found records of over a hundred cases in which this had led to gangrene, necessitating amputation.

Carbolic acid had a limited use as a caustic in the form of the liquefied preparation, and was less painful than most other caustics. It has also been employed in itching skin diseases, but is inferior to the cocaine series. Internally, it was at one time advocated as an intestinal disinfectant, but has been supplanted by less irritant and less soluble bodies. Its use as a remedy in constitutional diseases is now obsolete.

Poisoning.—In carbolic acid poisoning, when it has been taken by the mouth, the first treatment is the removal of the poison by the stomach tube and the thorough lavage of the stomach with water to which 10 per cent. of alcohol may be added; the alcohol dissolves the poison more readily than water and thus facilitates its removal, but has no other antidotal action, and should be removed from the stomach as completely as possible; when absorption has occurred from the skin or from a wound the dressing should be removed at once. The combination of phenol with sulphuric acid in the tissues forms a comparatively harmless body, and Baumann and Preusse therefore suggested the administration of sodium sulphate in large quantities. It is found, however, that this is of little or no use, because the phenol does not combine with sulphates as such in the body, but with organic sulphur compounds which are only in process of being oxidized to sulphuric acid. When coma and collapse set in, the patient is to be sustained by the application of warmth externally, and by the administration of such central nervous stimulants as caffeine, atropine or camphor; artificial respiration may eventually be used, although there is little prospect of resuscitation if the intoxication has advanced so far. The corrosion induced by carbolic acid locally may be treated by washing the part with alcohol, which dissolves the acid readily.

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Cresol.

The three cresols ($C_6H_4CH_3OH$) are nearly related to carbolic acid chemically and resemble it in their effects. Metacresol is less poisonous to mammals and less irritant, and at the same time seems to be more destructive to microbes than carbolic acid. Orthocresol is more dangerous than carbolic acid, and paracresol is the most powerful poison of all. In the presence of soaps the three cresols seem to be approximately equal in disinfectant power. A number of cases of suicidal poisoning with lysol have recently occurred, and in some of these marked alteration of the liver has been observed; nephritis and hæmolysis are also induced in some instances, but the chief symptoms arise from the central nervous system and consist in collapse and muscular exhaustion, followed by coma, thus closely resembling the effects of carbolic acid. Much of the cresol absorbed in cases of poisoning undergoes complete combustion in the tissues; the rest is excreted in the urine in combination with sulphuric and glycuronic acid and some in a partially oxidized form. The cresols are constituents of the tars and other crude antiseptic substances. They are only slightly soluble in water, and there has been some difficulty in rendering them available for surgical use, but this has been overcome by forming emulsions (*creolin*), or by dissolving them with the aid of salts (*solveol, solutol*), or suspending them by means of soap (*lysol*). These preparations are not devoid of poisonous properties, as is often stated; in fact, they are little, if at all, less dangerous than carbolic acid. They are used chiefly as surgical antiseptics, but creolin has also been given as an intestinal disinfectant, although with indifferent results. Their value as surgical antiseptics has been denied by some writers and there is no question that it has been much overrated by others.

Cresol (U. S. P.), a mixture of the three cresols, forms a colorless or straw-colored fluid with a phenol odor. Soluble in 60 parts of water. Dose, 0.05 c.c. (1 min.).

Liquor Cresolis Compositus (U. S. P.), Cresol 50 per cent. suspended in water by means of soap, is used in a diluted form as a surgical disinfectant.

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Thymol.

Another phenol homologue is thymol, which resembles carbolic acid closely in its action, though it causes less central nervous stimulation. Convulsions and tremors are rarely induced in either frogs or mammals, and when present, are very much less intense than those following carbolic acid. The animal generally sinks into a condition of apathy and weakness, which gradually passes into collapse and death. Thymol is less soluble in the fluids of the body, and is therefore absorbed more slowly than carbolic acid. It is also less irritant to wounded surfaces and is, according to most observers, considerably more poisonous to putrefactive organisms, while less poisonous to the higher animals. In poisoning from its use, fatty degeneration of the liver, marked congestion and even consolidation of the lungs, and irritation of the intestines have been observed. It is excreted in the urine in combination with sulphuric and glycuronic acids, partly unchanged, partly oxidized to thymolhydroquinone. There is also found in the urine a green coloring substance, which becomes blue on the addition of acid, and which seems nearly related to, but not identical with indigo. Thymol is said to be more liable to cause renal irritation than carbolic acid, and albumin and even blood have been repeatedly observed in the urine after its absorption.

Thymol (U. S. P., B. P.) ($C_6H_3C_3H_7CH_3OH$) occurs in common thyme and several other plants, and forms large, colorless crystals, which have the odor of thyme and are very insoluble in water. 0.125 G. (2 grs.) in pills, capsules, emulsion, or in solution in dilute alcohol.

Thymol has been used occasionally as an antiseptic lotion in $\frac{1}{10}$ per cent. solution, and as a mouth-wash and gargle, for which carbolic acid is rendered unsuitable by its unpleasant odor and its corrosive action. As an internal remedy it has proved a failure in the treatment of various constitutional diseases, such as acute rheumatism, phthisis and typhoid fever.

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It has recently been highly recommended as an anthelmintic for uncinaria or anchylostoma; it is given in capsules or emulsion in doses of 2 G. (30 grs.), repeated in two hours, and followed in six or eight hours by a brisk saline purge.

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Eucalyptol.

Eucalyptol ($C_{10}H_{18}O$) is the chief constituent of oil of eucalyptus, which is obtained from Eucalyptus globulus and some other species. It is also contained in the oil of cajuput and in other volatile oils. It has been recommended as a surgical antiseptic and in the same class of internal diseases as thymol, but does not seem to have any special virtues distinguishing it from the general class of volatile oils.

Eucalyptol (U. S. P.), a colorless fluid, having a characteristic, camphoraceous odor and a pungent, spicy, cooling taste. It is almost insoluble in water, but is miscible with alcohol in all proportions. Dose, 0.3 c.c. (5 mins.).

Resorcin.

The three dioxybenzols—resorcin, pyrocatechin and hydroquinone—resemble carbolic acid in their effects, but produce a more intense stimulation of the central nervous system, for convulsions have been observed in man after their use. This is especially true for the two last, resorcin being much less toxic than these. Resorcin seems to be equally or more strongly antiseptic than phenol, and is somewhat less poisonous, while the others are more dangerous; it is less irritant and caustic than carbolic acid. All three dioxylbenzols are excreted in the urine in combination with sulphuric and glycuronic acids. They are in part subjected to further oxidation, leading to coloration of the urine similar to that seen in carbolic acid poisoning. Pyrocatechin and hydroquinone when added to blood form methæmoglobin much more readily than phenol, and also tend to form it in the body when the intoxication does not progress too rapidly to allow of this alteration in the living animal. They cause a much greater destruction of the red blood cells than phenol.

Resorcinol (U. S. P.), resorcin, metadioxylbenzol ($C_6H_4(OH)_2$), colorless, very soluble crystals, with a faint aromatic odor. 0.125 G. (2 grs.).

Resorcin is a remedy which has fallen into almost complete disuse. At first introduced as an antiseptic, it was prescribed for a short time as an antipyretic, but has proved as unsuitable for this purpose as carbolic acid or aniline, which reduce fever temperature, but cause symptoms of collapse very readily. It has been used as an intestinal antiseptic and in rheumatic fever, but has here again been supplanted by less dangerous remedies. As an external application, it has been applied in ointment (5–10 per cent.) in skin diseases, and has been injected in cystitis and gonorrhœa in solution (1–3 per cent.), but in both cases is liable to produce irritation and pain. As an internal remedy it should be prescribed in dilute solution (1–2 per cent.).

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2. Pyrogallol.

Pyrogallol, the only trioxybenzol that has been largely used, produces nervous symptoms resembling those of carbolic acid, when given in very large doses to animals. In the cases of poisoning which have been observed in man, the symptoms closely resembled those caused by smaller quantities in animals, in that these nervous phenomena were almost entirely absent, and the poison acted not so much directly on the central nervous system as upon the blood corpuscles. Many of the other members of this series cause some destruction of the red cells, but none of them approach pyrogallol in the intensity of their effects. The red blood cells become shrunken and angular and lose most of their hæmoglobin, which escapes into the plasma and is changed into methæmoglobin; the blood therefore assumes a brownish-red color, which may be detected in the living animal by the discoloration of the skin and mucous membranes. If the intoxication is not too acute, icterus follows, and hæmoglobin and methæmoglobin are excreted in the urine. In the blood, fragments of red cells and "shadows," or red cells deprived of their coloring matter, are seen in large numbers, and the spectrum of methæmoglobin can be obtained easily. The kidneys are also affected, and the resulting nephritis is indicated by the presence in the urine of albumin, epithelium and casts, along with the products of the decomposition of the blood. The nephritis may lead to uræmic convulsions, which are sometimes accompanied by the nervous tremors characteristic of this series and also by dyspnœa and cyanosis from the lack of hæmoglobin in the blood.

The formation of methæmoglobin is generally believed to be connected with the well-known reducing properties of pyrogallol, but whether the methæmoglobin is a direct result of the reduction caused in the hæmoglobin, or whether a secondary oxidation accompanies this action, is unknown. Pyrogallol is excreted in part in combination with sulphuric acid in the urine, in part as unknown oxidized products, which give the urine a dark brown or black color, even when no blood pigments are contained in it. In fatal poisoning death seems to be due to the blood changes, and the consequent nephritis and jaundice, rather than to the direct effect of the drug on the central nervous system. It has been stated that the débris of the red blood cells fails to pass through the capillaries and thus leads to thrombosis, but this has been denied by later investigators.

The skin is dyed brown when pyrogallol is applied to it, from the products of oxidation formed.

Pyrogallol (U. S. P.), pyrogallic acid ($C_6H_3(OH)_3$), light, colorless crystals or laminæ when freshly prepared, which rapidly assume a darker color on exposure to light and air. It is very soluble in water and reduces the salts of the heavy metals even in the cold. It is used only externally.

Pyrogallol is used in the treatment of several forms of skin disease, especially in psoriasis, in which it is applied in ointment (5–20 per cent.). It is dangerous to apply it to very large surfaces, however, and many authorities therefore advise the use of chrysarobin in its stead. Pyrogallol ought never to be used internally. Its curative action in skin diseases may be due to its slight irritant and antiseptic properties, but is referred by some to its reducing action.

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3. Naphtalin and Naphtol (Naphthol).

Naphtalin and its compounds alpha- and beta-naphtol differ in some respects from the other members of the series. They are all insoluble in water, but the naphtols are dissolved in the alkalies. Some question has arisen as to whether **Naphtalin** is really an antiseptic in itself, or whether it owes its activity to the formation of the more soluble naphtols. Animals poisoned with it do not exhibit the ordinary symptoms of poisoning with an aromatic body, even when it is administered for several weeks, but suffer from diarrhœa and lose flesh rapidly, either from disturbance of the alimentary canal or from renal disorder. The urine soon contains albumin, casts and epithelium, and the kidney is found in a condition of parenchymatous nephritis. The changes in the eye caused by naphtalin and naphtol have excited some interest. The retina is seen with the ophthalmoscope to be dotted over with numerous bright points, or sometimes to contain large yellow plaques, and after large doses subretinal effusion has been observed. At the same time atrophy of the optic nerve may occur, and bright points are seen in the vitreous humor similar to those in the retina. A slight cloudiness appears in the lens and increases rapidly until it becomes opaque and resembles an ordinary cataract in man. This does not seem to be secondary to the retinal changes, but is the result of an inflammatory infiltration beginning in the ciliary body and iris and extending into the lens and finally into the posterior surface of the cornea. These changes in the eye have generally been observed in animals treated with large doses of naphtaline or naphtol, and have not occurred in such intensity in man; but v. d. Hoeve states that commencing retinal degeneration may be induced in man by the use of naphtol internally or externally, and cautions against its prolonged administration.

Large doses of the **Naphtols** induce symptoms similar to those of carbolic acid poisoning, except that in the dog no convulsions have been observed, and in the other mammals they seem less pronounced. They are irritating to the mucous membranes when they come in contact with them in solution or in vapor; thus they cause sneezing and coughing when applied to the respiratory passages, and in the course of excretion induce pain in the bladder and urethra with strangury and swelling of the mucous membrane. Injected subcutaneously or absorbed from the alimentary canal in animals, they induce acute nephritis with the appearance of albumin and hæmoglobin in the urine, and some nephritis has been caused in man from their external application. They seem to have less effect on the circulation and respiration than the other aromatic antiseptics, but resemble them in tending to destroy the red cells of the blood. Alpha-napthol has been found to be more strongly antiseptic than the beta compound, and may be more poisonous, as is generally stated, but no satisfactory investigation has appeared regarding this point. Beta-naphtol is several times as strongly germicidal as carbolic acid, and is the form used in therapeutics.

Naphtalin is partly oxidized in the tissues and appears in the urine as alpha- and beta-naphtol and naphtoquinone, all in combination with glycuronic and sulphuric acid. The naphtols are excreted in combination with these acids also. These bodies and their oxidized products give the urine a reddish-brown tint, which may become deeper on exposure to the air, but in some cases it retains its ordinary color.

PREPARATIONS.

Naphthalenum (U. S. P.), naphtalin or naphtalene ($C_{10}H_8$), colorless, insoluble crystals with a coal-tar odor and a hot, aromatic taste. 0.125 G. (2 grs.).

BETANAPHTHOL (U. S. P.), NAPHTHOL (B. P.), Beta-naphtol ($C_{10}H_7OH$), white or yellowish-white, insoluble crystals or powder, with a faint phenol odor and a hot taste. 0.25 G. (4 grs.).

Therapeutic Uses.—Naphtalin and naphtol were at first introduced as external applications in parasitic skin diseases of various forms, but have been more extensively prescribed as intestinal disinfectants. In some disorders, such as diarrhœa, in which the walls of the intestine are only secondarily affected by the putrefaction of the contents, they have proved efficacious, but when the intestinal walls themselves are the seat of the primary disease, as in typhoid fever and dysentery, they are of doubtful value. They have been employed as anthelmintics to a limited extent, and apparently with some success, though they have not proved so reliable as some of the older drugs used for this purpose. Naphtol is more largely used than naphtalin in internal medication, and may be prescribed as a powder or in capsules. They are used externally as ointments (5–10 per cent.). Naphtalin and naphtol ought to be avoided in irritation of the kidneys, bladder or urethra.

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4. Tar.

The action of the various crude preparations of the antiseptic series resembles that of the pure principles, but as in most of them the creosols, guaiacols and others less poisonous aromatic compounds are present in larger quantity than the phenols and dioxybenzols, they are less poisonous than carbolic acid and its simpler homologues. At the same time these higher combinations do not seem to be much less antiseptic than the simpler benzol derivatives, so that several of the crude preparations possess considerable value in surgery and medicine.

PREPARATIONS.

Pix Liquida (U. S. P., B. P.), tar, is obtained from the wood of Pinus palustris and other species of Pinus by destructive distillation and contains a very large number of aromatic bodies mixed with others of less importance.

Oleum Picis Liquidæ (U. S. P.), oil of tar, is a volatile oil distilled from tar, and is similar to creosote, except that it consists almost entirely of guaiacols and their compounds. 0.2 c.c. (3 grs.).

Syrupus Picis Liquidæ (U. S. P.), syrup of tar, 4 c.c. (1 fl. dr.).

Unguentum Picis Liquidæ (U. S. P., B. P.).

Oleum Cadinum (U. S. P., B. P.), oil of cade or empyreumatic oil of juniper, is obtained by dry distillation of juniper wood, and contains dioxylbenzol and guaiacol combinations. It is less strongly disinfectant than the other tars.

Tar is a valuable disinfectant, which is very generally available and is much cheaper than the purer bodies of the aromatic series. It may be used for the disinfection of excrementa, latrines, etc., where the cost of even crude carbolic acid would be prohibitive.

Tar has also been used with considerable success as an antiseptic in skin diseases, in which it may be applied either alone or as an ointment. It is only slightly irritating to the skin, and some absorption occurs, as is often seen by the dark color of the urine. Internally it has been used occasionally as an anthelmintic and intestinal disinfectant, much more frequently as an "expectorant" in cough mixtures. Whether it has any effects on the lungs or not in these cases may be questioned. It is generally given as the syrup.

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Creosote.

Creosote may be regarded as a wood-tar from which the more poisonous phenols and the less volatile bodies have been eliminated, leaving guaiacols and creosols as the chief constituents. Its action is similar to that of carbolic acid, except that it has less tendency to induce nervous symptoms, and is less irritant and poisonous. On the other hand, it seems at least as strongly antiseptic as carbolic acid, and according to some investigators far excels it as a germicide.

PREPARATIONS.

Creosotum (U. S. P., B. P.) is obtained from wood-tar, preferably from beech tar, and is an almost colorless oily liquid with a smoky odor and hot, burning acrid taste. It is slightly soluble in water, but mixes readily with alcohol. It tends to darken in color when exposed to the light. 0.05–0.3 c.c. (1–5 mins.).

Aqua Creosoti (U. S. P.), a very dilute solution of creosote in water, less than one per cent. 8 c.c. (2 fl. drs.).

Unguentum Creosoti (B. P.).

Creosote may be administered in pills, capsules, in solution in alcohol or cod-liver oil, or as a mixture. The wine of creosote, which has been a popular remedy, contains it dissolved in wine along with some brandy and tincture of gentian. It ought not be allowed to reach the mucous membranes in a concentrated form, as it is liable to irritate them.

Therapeutic Uses.—Creosote is comparatively seldom used except in the treatment of pulmonary phthisis and gangrene, and chronic bronchial inflammation. It is generally given by the mouth in these cases, but has also been injected hypodermically or into the rectum; the vapor is recommended as an inhalation, and some practitioners have injected creosote solution into the trachea, in order to ensure its reaching the lungs. None of these methods are believed to give such good results as the ordinary administration by the mouth.

The results of creosote medication are still disputed. Many clinicians state that a general improvement follows it in phthisical patients, that the appetite is improved, the cough and expectoration lessened, and that the patient feels stronger and better. On the other hand, others are extremely sceptical as to any benefits arising from creosote, and regard it as merely one of the countless remedies which have been recommended in this condition, and which after a shorter or longer period of popularity have passed into oblivion.

It is generally supposed by the advocates of the creosote treatment that the remedy destroys the tubercle bacillus in the lungs through its antiseptic properties. On the other hand, animals infected with tubercle and treated with creosote die as soon as controls which are untreated, and the sputum of phthisical patients treated with creosote is as virulent as that of others not so treated. Besides, the administration of creosote by other ways than by the mouth is said to be very much less efficacious. Another explanation of the creosote action is that it acts as an intestinal antiseptic and prevents the secondary infection of the bowel; but it has been objected to this that the other intestinal antiseptics are of little value in tuberculosis. It seems useless to speculate on the method of action until it has been definitely determined that creosote is of value in phthisis, and this can be done only by careful statistical inquiry. The medical profession seems to have much less faith in the efficacy of the creosote treatment than it had a few years ago, when it was not generally recognized that pulmonary tuberculosis is curable by hygienic measures in a considerable proportion of instances.

Creosol, an ether of dioxytoluol, is contained in creosote and other wood-tars, and has, as far as is known, effects similar to those of the allied bodies, but has not been investigated so carefully as some of the others.

Guaiacol, the methyl ether of pyrocatechin, seems to be somewhat more poisonous than carbolic acid according to Marfori, whose preparations, however, were by no means pure; the symptoms induced were those characteristic of the series. It is excreted in the urine in combination with sulphuric and glycuronic acids.

Guaiacol Carbonate seems to have the same effects as guaiacol, into which it is decomposed in the intestine.

It was found a few years ago that guaiacol applied to the skin over a sufficiently wide area produced a marked fall of temperature in fever, but this does not seem to be any specific effect of guaiacol, and would probably have resulted from the application of any other equally volatile member of the group. The explanation is that a certain proportion of the guaiacol applied is absorbed from the skin, and the fall of temperature is one of the symptoms of poisoning. Considerable quantities of guaiacol have been recovered from the urine after this method of medication. The fall of temperature is generally abrupt and is accompanied by some exhaustion and weakness, and by profuse perspiration. The temperature soon rises again to its former height with shivering and rigors, and there seems good reason, therefore, why guaiacol should not be classed among the more satisfactory antipyretics.

Guaiacol (U. S. P.) ($C_6H_4 \cdot OH \cdot OCH_3$), colorless crystals, or fluid with an agreeable aromatic odor, soluble in 53 parts of water and in alcohol. Dose, 0.5 c.c. (8 mins.).

Guaiacol has been administered as a substitute for creosote in tubercular disease. It is generally given in solution in alcohol or cod-liver oil, or in pills. It has been injected hypodermically.

Guaiacolis Carbonas (U. S. P.) ($(C_7H_7O)_2CO_3$), an almost tasteless powder; is given in cachets in doses of 0.2–0.5 G. (3–8 grs.) in pulmonary phthisis.

Ichthyol is derived from the tar of a bituminous shale which is found in the Tyrol, and which contains the remains of many fossil fishes. It has a high percentage of sulphur, which seems to be only in part in the form of sulphons, in part in that of mercaptans and sulphides. It possesses some antiseptic action, although it is believed to be less powerful than carbolic acid. Applied to the skin, ichthyol causes slight irritation, which is apparently of benefit in some cutaneous diseases, and it has therefore been used extensively for this action. A certain amount of absorption occurs when it is rubbed into the skin, for the sulphur of the urine has been found to be augmented. Taken internally in large quantities, it acts as a gastric and intestinal irritant and produces diarrhœa, but it is only very feebly poisonous.

Ichthyol has been strongly recommended in the treatment of a number of skin diseases, including erysipelas. It is generally used as an ointment containing equal parts of ichthyol and of vaseline, but may be used in ten per cent. or even weaker dilution. Ichthyol has in the last few years been enthusiastically praised as a remedy in the most diverse conditions, and it seems probable that its sphere of utility will be very much more restricted in the future, if it does not disappear from therapeutics entirely.

5. Salicylic Acid.

Salicylic acid differs from phenol chiefly in being very much less poisonous to the higher animals, while it is practically of equal antiseptic value, provided the conditions are favorable. The salicylates produce the same effects as the free acid, excepting that they are much less irritant to the skin and mucous membranes. It was formerly stated that the salicylate of soda, which is the only salt that has been largely used, was devoid of antiseptic action, but this has been shown to be incorrect.

Antiseptic Action.—Salicylic acid retards the digestion of proteins by the gastric and pancreatic juices, and the decomposition of glucosides by the unorganized ferments, but how far this effect is due to the free acid and how far to a specific antiferment action cannot be definitely stated. The putrefaction of protein solutions and the alcoholic and acetic acid fermentations are also retarded, or entirely prevented by the presence of comparatively small quantities of salicylic acid or of the salicylates. They offer some points of contrast with carbolic acid, however, for it is found that if much proteid be present the salicylic preparations are generally less efficient than phenol; this is perhaps due to the phenol being volatile and therefore penetrating more readily and forming less stable combinations with the protein. Salicylic acid, on the other hand, does not evaporate and therefore preserves bodies which are exposed to the air for a longer time than carbolic acid, which is soon dissipated. These considerations may perhaps explain the very different results which have been obtained by different observers in regard to the comparative germicidal power of these substances. The movements of plant protoplasm, protozoa and leucocytes are prevented by salicylic acid as by quinine and the other aromatic antiseptics.

Irritant Action.—Salicylic acid is much less irritant than phenol, but when it is applied for some time as a powder to wounds, mucous membranes, or even the skin, it may induce the same corrosion and necrosis as have been mentioned under carbolic acid. In solution it has a destructive action on the horny layer of the epidermis, which becomes softened and easily removed, without any noticeable irritation having been induced. It sometimes causes soreness and irritation of the mouth and throat when swallowed in powder, and congestion and even erosion of the mucous membrane of the stomach have been observed. In dilute solution, however, the acid has no such effect, and even comparatively concentrated solutions of the salts seem almost devoid of corrosive properties.

Symptoms.—Salicylic acid and its salts are rapidly absorbed from the stomach and intestine and as a general rule produce no symptoms, unless when given in very large doses. Some individuals, however, are peculiarly sensitive to the action of salicylic acid, and in these, comparatively small doses are followed by symptoms which are generally of only slight importance, but which are sometimes sufficiently grave to cause anxiety, and in very rare cases have been followed by death.

The ordinary symptoms are a feeling of heaviness and fulness in the head, with hissing or roaring sounds in the ears exactly resembling those produced by quinine. These may be followed by some confusion and dulness and by indistinct sight and hearing. Very often the patient complains of excessive perspiration and a sense of warmth all over the body. Dyspnœa, marked by exceedingly deep and labored respiration, has been noted in more serious cases of poisoning, and a condition of collapse with slow, weak pulse, subnormal temperature and partial or complete unconsciousness may follow. In others delirium and hallucinations of sight and hearing have occurred, these being more frequently seen in chronic alcoholic patients and in cases of diabetes than under other conditions. Albumin, casts and even hæmoglobin and blood in the urine have been noted as sequelæ. Various forms of skin eruptions have been described as occurring under the use of salicylic acid, sometimes after a single dose, but much more frequently after prolonged treatment. They resemble those seen under the antipyretics, but seem to be less frequently elicited by salicylic acid. Abortion has been repeatedly observed under salicylate treatment, but it seems open to question whether this was due to the remedy or to the disease. Hæmorrhages from the uterus, nose, mouth and intestine have also been credited to the action of this drug. Numerous other symptoms have been noted after it, but so rarely that a doubt may be entertained as to whether they were not due to some special condition, or perhaps to some impurity in the drug.

In animals salicylic acid injected intravenously causes some acceleration of the pulse and respiration, followed by slowness and weakness of the heart, and often by marked dyspnœa. Depression of the central nervous system is shown by slowness, weakness and incoördination of the spontaneous movements, and eventually by stupor and arrest of the respiration, which is generally preceded by convulsions. Photophobia and clonic spasms have been observed in some dogs.

Hyperæmia of the kidney, liver, brain and tympanum are sometimes found at the autopsy on dogs poisoned with salicylic acid, and when the drug has been given in powder, congestion, irritation and necrosis of the gastric mucous membrane. This irritation of the stomach often causes vomiting in dogs, and the poison being thus eliminated, no further symptoms appear.

In the frog salicylic acid produces quickened respiration and increased reflexes, followed by depression of the spontaneous movements, tremor and clonic contractions. The heart is slow, dilated and weak.

The symptoms elicited by salicylic acid and its salts are therefore very indefinite, and with few exceptions occur so seldom in man that they may be discussed very shortly.

The **Disorders of Hearing** have been ascribed to congestion of the tympanum, but may perhaps indicate some changes in the nerve cells of the ear analogous to those observed under quinine. As a general rule they pass off in the course of a few hours or days, but they sometimes leave a more or less permanent impairment of the sense of hearing. The **Dimness of Sight**, sometimes amounting to complete blindness, is due to vascular or retinal changes in the eye (see Quinine), and some disturbance of the circulation of the brain and head may be the cause of the dulness and fulness of the head complained of and of the not infrequent epistaxis. Maragliano showed by plethysmographic measurements that the **Vessels of the Skin** are dilated by salicylic acid in the same way as by the antipyretics. The exact mechanism by which these alterations in the distribution of the blood are produced, is unknown, but the most probable explanation would seem to be that the vaso-dilator centres in the medulla controlling these areas are excited.

The general **Blood-Pressure** is found to be increased by small quantities of the salicylates from stimulation of the vaso-constrictor centre, while after very large injections into the blood vessels, the pressure is lowered, partly perhaps from depression of the centre, but mainly from the cardiac action of the drug.

Small quantities are found to accelerate the **Heart** in animals in the same way as small doses of the other aromatic bodies, apparently from direct action on the cardiac muscle. Very large doses produce a slow, weak and dilated heart, and a corresponding fall in the blood-pressure.

The acceleration of the **Respiration** and the dyspnœa which have been noted occasionally in man, seem to be due to some central action. In animals the respiration is first accelerated to some extent, and then slowed, apparently from the respiratory centre being first excited and then depressed, and eventually paralyzed by very large quantities of the drug. Death seems to be due to this paralysis, the heart continuing to beat for some time afterwards.

The effects of salicylic acid on the **Central Nervous System** seem to be comparatively slight, except in cases in which a special idiosyncrasy exists. No such convulsive action as occurs under others of the aromatic series has been observed under it and in animals there seems no marked depression save in the medulla oblongata. The convulsions which are observed before death are probably not due to the direct action of the drug, but to the asphyxia. In the medulla oblongata the respiratory and vaso-constrictor centres, and probably the vaso-dilator, seem to be first stimulated and then depressed. In the frog depression and paralysis of the spinal cord are produced by large doses.

The **Perspiration** which so often follows the administration of salicylic preparations may be due in part to the dilatation of the skin vessels, but is probably to be ascribed rather to increased activity of the sweat centres. Some of the **Skin Rashes** may also be caused by the dilatation of the cutaneous vessels, and perhaps in all cases this may be looked upon as a favorable condition, which leads to eruptions in individuals who are predisposed to them.

The peripheral **Muscles and Nerves** do not seem to be more affected by salicylic acid than by the other members of the series.

Salicylic acid and its salts increase to some extent the **Secretion of the Urine**, probably through a direct action on the renal epithelium, although the increased formation of urea may also play a part in the slight diuresis. Irritation of the kidney and nephritis are observed in some cases, with the appearance of albumin and blood in the urine.

The salicylic preparations produce a slightly augmented flow of **Bile**, apparently from some specific action on the liver cells. The bile is generally more dilute than normal, the fluid increasing more than the solids, though the total solid excreted is augmented.

Salicylates have been said to lower the normal **Temperature**, but this seems to be erroneous, except when very large quantities produce a condition akin to collapse. Some of the results may also be due to the use of impure preparations. In fever patients, however, it often causes a marked fall of temperature, and it was formerly used as an antipyretic for this reason. The action is probably explained by the dilatation of the cutaneous vessels and the increase in the output of heat. (See Antipyretics.) Dilatation of the skin vessels also occurs in normal persons after salicylates, but this is probably counterbalanced in them by increased heat formation. The fall in temperature after salicylic acid is generally less in extent and of shorter duration than that following the members of the antipyrine series.

In its passage through the tissues, salicylic acid modifies the **Metabolism**, as is shown by an increase of 10–12 per cent. in the nitrogen and sulphur of the urine. This indicates a considerably augmented decomposition of the proteins of the body, but whether it is accompanied by increased oxidation is unknown. A still more notable augmentation of the uric acid excreted has been observed, different authors estimating it at 30–45 and even 100 per cent. This occurs also in animals and persons on a purine-free diet, so that it is obviously due to changes in the endogenous purine metabolism, probably arising from salicylates retarding the destruction of uric acid in the tissues. The number of leucocytes in the blood has been found to undergo a corresponding increase.

The form in which salicylic acid circulates in the blood was formerly the subject of some discussion, owing to the erroneous belief that its salts were devoid of antiseptic action. It is now known to exist in the blood as the salicylates of the alkalies. It is said to accumulate in large quantities in the cavities of the **Joints**, being taken up from the blood by the synovial membranes and secreted into the synovial fluids; this has probably a bearing on its specific action in acute rheumatic fever. It is **Excreted** by the kidneys, for the most part in a combination with glycocoll, which is known as salicyluric acid, and which is strictly analogous to hippuric acid. Salicyluric acid seems practically inert, and has no effect in acute rheumatism. Some of the salicylic acid is excreted uncombined. It appears in the urine within an hour of its administration by the mouth and is all eliminated in 48 hours. It has also been found in the milk, perspiration and bile, but does not appear to be excreted into the stomach.

Several compounds which owe their virtues to the salicylic acid radicle are used in medicine, and all produce similar results after absorption, but vary in their local action. **Methyl Salicylic Ester**, which occurs in many plants and forms some 90 per cent. of the oil of winter-green, and almost the whole of the volatile oil of birch, has a hot, burning taste, and like other volatile oils produces a feeling of warmth in the stomach. In many cases it is well borne, but some patients complain of pain in the stomach, loss of appetite and even nausea and vomiting. It is rapidly absorbed and produces the characteristic symptoms of salicylic acid in large doses, roaring sounds in the ears and more or less deafness. It is partly excreted as salicyluric acid, the decomposition probably occurring mainly in the intestine.

Salol, the phenyl salicylic ester, is a very insoluble, crystalline body, which has little or no local action in the mouth or stomach, but is decomposed in the intestine by the fat-splitting ferment of the pancreatic juice. Some decomposition also appears to occur in the stomach, at any rate under certain conditions. The products of its decomposition, salicylic and carbolic acids, are absorbed and produce their usual effects. Salol is used chiefly as a substitute for salicylic acid, but the formation of phenol from it in the body must not be overlooked, for in several cases of dangerous poisoning which have been observed under it, the symptoms were those characteristic of carbolic acid, and the urine became dark in color from the phenol oxidation products. In moderate quantities, salol produces the disturbances of hearing observed under salicylic acid, without any symptoms of carbolic poisoning.

Other salicylic acid compounds, similar to salol, are *betol* or *naphtalol* (the beta-naphtol salicylate), *cresalol* (cresol and salicylic acid), *thymosalol* (from thymol), *guaiacolsalol.* They are less poionous than salol, and may be used for most purposes as substitutes for salicylic acid, but are less active antiseptics.

Salicin, a glucoside found in many species of willow and poplar, is decomposed into salicylic alcohol, which is oxidized to salicylic acid in the body, so that its action after absorption is similar to that of the acid. It is unknown whether the decomposition occurs in the alimentary canal or in the tissues, but from the fact that it is excreted mainly as salicin when it is injected intravenously, it would seem probable that the decomposition, like that of the ordinary esters, takes place chiefly in the intestine. It is very bitter, but does not irritate the mucous membranes, and is not so certain in its action as salicylic acid and some of its esters. When administered by the mouth it is excreted in the urine partly as salicin, partly as saligenin or salicyl alcohol, and partly as salicylic and salicyluric acids.

Preparations.

Acidum Salicylicum (U. S. P., B. P.), salicylic acid ($C_6H_4OHCOOH$), small, white, needle-like crystals, or a light crystalline powder, odorless with a sweetish, afterwards acrid, burning taste, slightly soluble in water, very soluble in alcohol or ether. A reddish tinge indicates the presence of carbolic acid or other impurities, and salicylic acid for internal use ought to be entirely colorless.[1] Salicylic acid is much more soluble in solutions of neutral salts, such as the borates or citrates, than in pure water. 0.3–2 G. (5–30 grs.). It is generally given in capsules or tablets.

Unguentum Acidi Salicylici (B. P.), 2 per cent.

Sodii Salicylas (U. S. P., B. P.), sodium salicylate ($C_6H_4OHCOONa$), a white, odorless powder with a sweetish taste, very soluble in water, less so in alcohol. 0.6–2 G. (10–30 grs.) in capsules or tablets, or dissolved in syrup.

Oleum Gaultheriæ (U. S. P.), oil of wintergreen, a colorless or yellowish fluid with a characteristic, pleasant odor and a sweetish, aromatic taste, insoluble in water, soluble in alcohol, contains 90 per cent. of methyl salicylate. 1 c.c. (15 mins.) in emulsion or capsules.

Oleum Betulæ (U. S. P.), oil of sweet birch.

Methylis Salicylas (U. S. P.), artificial oil of wintergreen ($C_6H_4OHCOOCH_3$), is practically identical with the oil of sweet birch and forms 90 per cent. of the oil of wintergreen. It may be prescribed in the same doses and forms as the latter.

Spiritus Gaultheriæ (U. S. P.) is used as a flavor chiefly. 2 c.c. (30 mins.).

Salicinum (U. S. P., B. P.), salicin ($C_6H_{11}O_5OC_6H_4CH_2OH$), a glucoside obtained from several species of willow and poplar, consists of white, silky, crystalline needles, with a very bitter taste, soluble in 28 parts of water. It is decomposed by ferments into glucose and saligenin or salicyl alcohol ($C_6H_4OHCH_2OH$). 0.5–2 G. (8–30 grs.) or more every 3 or 4 hours, given in powder, capsules or in solution, which, however, is very bitter.

Salol (B. P.), Phenylis Salicylas (U. S. P.), phenyl salicylate ($C_6H_4OHCOOC_6H_5$), a white crystalline powder, odorless or faintly aromatic, almost tasteless, almost insoluble in water, decomposed by the pancreatic juice into salicylic acid and phenol. 0.5–2 G. (5–30 grs.) in powder or capsule.

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[1] Salicylic acid formed synthetically from phenol is often said to be more poisonous than that obtained from the oil of wintergreen (methyl salicylate), but this is due, not to any difference in the acid, but to the presence of carbolic acid and other impurities in the artificial preparation.

Aspirin or acetylsalicylic acid ($C_2H_3O—OC_6H_4COOH$) is very slightly soluble in water and has a more pleasant acid taste than salicylic acid, but offers no further advantages over it. It is decomposed into salicylic acid in the intestine. It has appeared under numerous designations of late years and much exaggerated claims have been made for it as a remedy for most diverse conditions. Dose, 2–3 G. (30–40 grs.).

Therapeutic Uses.—Salicylic acid and the salicylate of soda were at one time used to a considerable extent as antiseptics in surgery, and indeed promised to supplant carbolic acid for this purpose, as they were less irritating and also less poisonous. They have been less used of late years, and although bacteriological experiment has shown that the acid is at least as destructive to the pyogenic organisms as carbolic acid, most surgeons find it less satisfactory in practice.[1]

Salicylic acid is occasionally applied locally in excessive sweating, and has also been used in various skin affections in which it is desirable to soften or partially dissolve the epidermis. Both acids and salts are absorbed too rapidly to act as intestinal disinfectants.

In 1875 it was found to have antipyretic properties, and for a few years it was used as a general antipyretic in fever, but has been entirely supplanted for this purpose by the more recently discovered antipyrine series. It was also suggested as a substitute for quinine, but has no specific action on the malarial organisms.

The chief sphere of usefulness of salicylic acid at the present time is in the treatment of acute rheumatic fever, in which it seems to have a specific action only excelled by that of quinine in malaria. Other members of the aromatic series have some effect in this condition, but none of them equal the salicylic preparations in efficacy. Under this treatment the pain and swelling in the joints rapidly lessen, the temperature often falls, and the course of the disease is shortened. It is still debated whether the salicylic treatment reduces the liability to endocarditis and pericarditis, which are common complications of acute rheumatic fever; some clinicians even state that it increases the risk of these complications, while others advise the discontinuance of the treatment when any symptoms arise from the heart. The view more generally entertained, however, is that the cardiac affections are less often met with and are less severe under salicylic treatment, and very often it is continued in small quantities even after the heart is undoubtedly involved in the disease. The remedy sometimes fails in rheumatism, as quinine does in malaria, and it sometimes acts more satisfactorily in one joint than in another. Large doses (1–2 G. or 15–30 grs.) repeated every 2–3 hours are necessary in some cases at first, the quantity being reduced as the symptoms abate. Salicylic acid is less frequently used than the salicylate of sodium. Alkaline carbonates are sometimes recommended along with the salicylate, on the ground that they promote the excretion of salicyluric acid and prevent the appearance of symptoms of poisoning. Oil of wintergreen may also be used here, but, like salicylic acid, is more liable to cause gastric irritation. When high fever is present the antipyretic combinations of salicylic acid, such as malakine, may be used with advantage. Salicin is less disturbing to the stomach than the other preparations, but is less certain in its effects and has to be given in larger quantities.

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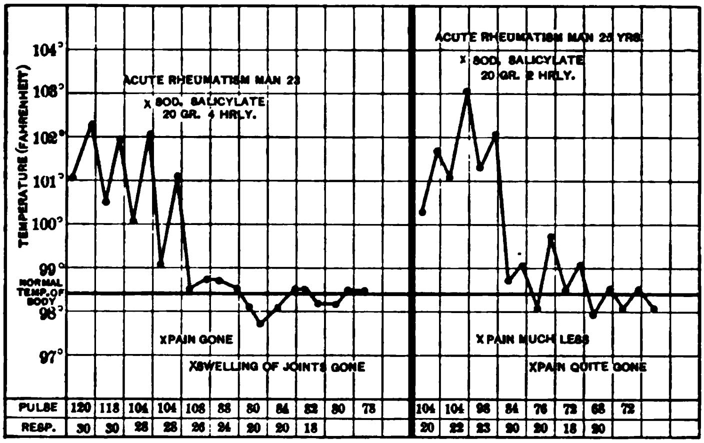
[1] Salicylic acid has been used very largely as a preservative in wine and beer. No evil effects have been definitely shown to follow the prolonged use of liquors thus treated, but it is not impossible that they may be injurious, and several governments have found it advisable to prohibit its use for this purpose.

FIG. 58.



Clinical charts of cases of acute rheumatic fever treated with salicylate of sodium. Case 1, 20 grains every four hours; Case 2, 20 grains every two hours. (STOCKMAN.)

In other acute constitutional diseases accompanied by fever, salicylate has no such specific action as in acute rheumatic fever; this suggests that in the latter it acts on the cause of this malady with especial power, or perhaps that it is put in a favorable position by being secreted into the joints which are the seat of the infection.

Salicylic acid has also been used in the various forms of disease which are roughly classified as rheumatic—chronic rheumatism, arthritis, neuralgia, myalgia—but the effects are less satisfactory than in acute rheumatism.

Salicylic acid in some cases promotes the absorption of effusions into the serous membranes, such as the pleura, and also subretinal effusion. It is unknown how this is effected, but it scarcely seems probable that the slight diuretic action of the drug is sufficient to account for it.

The cholagogue action of the salicylates is quite inconsiderable in comparison with that of the bile itself, and in any case in which an increase of the bile secretion is desirable, recourse should be had rather to the latter. It has recently been suggested by Kuhn that the salicylic salts excreted in the bile may retard the growth of microbes and thus prove of value in the treatment of liver and gall-bladder infections.

The solubility of the salicylates and their rapid absorption precludes their use as intestinal antiseptics, but salol has been used to lessen putrefaction in the bowel, and even to act upon the bacilli of typhoid fever and of tubercle infecting the intestinal wall. Kumagawa, however, states that the putrefaction in the bowel as measured by the indican in the urine is unchanged by its administration, and he found enormous numbers of bacteria in the fæces afterwards. It certainly seems of little value in typhoid fever or in tuberculosis of the intestine. Intestinal calculi have been formed in a few instances from prolonged treatment with salol, which failed to be decomposed in the intestine and formed masses of considerable size.

Salol was at one time supposed to be absorbed only after its decomposition in the intestine by the pancreatic juice, and Ewald therefore suggested its use as a means of diagnosing stenosis of the pylorus. He supposed that in cases in which the food was delayed or prevented from passing into the intestine, the reaction of salicylic acid in the urine would appear correspondingly late or be entirely absent. But some salol seems to be absorbed from the stomach, and, on the other hand, the interval between its administration and the appearance of the salicylic reaction in the urine is so variable in normal individuals that the test is of little value. Salol has been used to coat pills and prevent their solution in the stomach.

Salol has some value as a genito-urinary disinfectant, partly owing to the salicylic acid component and partly to the phenol developed.

It is used as a substitute for salicylic acid in rheumatic fever, as has been mentioned, and has the advantage of being tasteless and of producing no irritation in the stomach. On the other hand, the considerable amount of carbolic acid freed by its decomposition has given rise to poisoning in some cases. Externally it is of little or no value as an antiseptic, as it is only active when decomposed by the microbes which it is designed to destroy.

Salicin is used as a substitute for salicylic acid only in rheumatic fever. It has been prescribed as a stomachic bitter.

Salicylic preparations have to be used with care where any symptoms of renal irritation are present. In cases of poisoning, the treatment is determined entirely by the symptoms, and no antidote is known. Glycocoll has been suggested for the same reason as the sulphates in phenol poisoning, but would presumably be of no greater value.

Methyl salicylate, or oil of wintergreen, is often applied locally in muscular and articular rheumatism, it being supposed that larger quantities thus reach the focus of disease than when the drug is taken by the mouth. Absorption certainly occurs through the skin, as is proved by the appearance of salicyluric acid in the urine. But irritation of the skin is liable to be excited, and the value of the salicylates is doubtful in these diseases. Mesotan, or methoxymethylsalicylate, has been introduced as a substitute for oil of wintergreen in external treatment, but has no advantages of any consequence over the older drug.

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Other Aromatic Oxy-acids.

The two isomers of salicylic acid, *meta-* and *para-oxybenzoic acid,* are said to be almost devoid of antiseptic properties, and, although some doubt may be entertained as to the correctness of this statement, they have never been used in medicine except experimentally.

The *cresotinic acids* resemble salicylic acid in their effects, and the paracresotinate of soda has been used occasionally as an antipyretic and substitute for salicylic acid. The metacresotinate is very much less active, while the orthocresotinate possesses a dangerous action on the heart. The paracresotinate is somewhat less poisonous than salicylic acid. The cresotonic acids are found as impurities in some commercial specimens of salicylic acid, but these ought not to be used for internal administration, as the presence of the orthocresotonic acid may affect the heart.

The *alpha-* and *beta-oxynaphtoic acids* are possessed of antiseptic properties, which are said to be somewhat greater than those of carbolic and salicylic acids, but they are less soluble in water, while the sodium salt is less antiseptic. The acids are irritant and produce diarrhœa and symptoms similar to those of salicylic acid. They seem to be at least as poisonous as carbolic acid, and have been used as external antiseptics only to a very limited extent.

Sulphocarbolates.

The sulphon group lessens the toxicity in the same way as carboxyl, and the sulphocarbolates or para-phenol-sulphonates are therefore less poisonous than carbolic acid. The sulphocarbolates of sodium and zinc have been used as external antiseptics, and the sulphocarbolate of sodium has been administered to arrest fermentation in the stomach. The zinc salt possesses some astringent action and has been used with good results as an injection in gonorrhœa. The sodium salt is probably excreted in the urine unchanged. *Aseptol* or *sozolic acid* is a 33 per cent. solution of orthophenol-sulphonic acid in water but very often contains some of the para-acid. Of the three phenol-sulphonic acids, the ortho- is the most strongly antiseptic and the para- the least useful.

Sodii Sulphocarbolas (B. P.), *Sodii Phenolsulphonas* (U. S. P.), or sodium para-phenol-sulphonate ($C_6H_4OHSO_2ONa, 2H_2O$), forms colorless, transparent prisms, without odor, and with a saline taste. Soluble in 5 parts of water. 0.3–1 G. (5–15 grs.).

Zinci Sulphocarbolas (B. P.) ($Zn(OHC_6H_4SO_3)_2H_2O$) forms colorless, transparent, efflorescent crystals, which are very soluble in water and in alcohol.

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Benzoic Acid.

Benzoic acid possesses almost the same action as salicylic acid in the body, and, like it, is poisonous only in comparatively large quantities. It seems to be equally, or according to some observers, more strongly antiseptic, and like salicylic acid irritates the mucous membranes, while its salts are practically devoid of this last property. Benzoic acid is, however, apparently less stimulant to the central nervous system, and the characteristic affections of the hearing and sight have not been observed under it.

In man very large quantities of benzoic acid and also of the benzoate of soda sometimes produce nausea and vomiting, the vomited matter rarely being tinged with blood. A certain sedative action on the central nervous system is also said to be observed, and an increased expectoration of mucus is produced in cases of bronchial irritation. The pulse is somewhat accelerated.

In the dog tremors and convulsions have been observed, but are generally less marked than under carbolic acid. Ataxia, paresis and eventually complete paralysis of the fore limbs, and later of the hind limbs and trunk follow, the temperature falls, and death occurs from asphyxia. The heart and respiration are first accelerated and then slowed, from a direct action on the heart and on the respiratory centre. Vomiting occurs when the acid or the salts are given by the mouth. Post-mortem the gastric mucous membrane has been found to be eroded and ecchymosed, even when the salts or acid have been injected subcutaneously or intravenously, so that the benzoates and benzoic acid would seem to have a specific action on the gastric mucous membrane quite apart from their irritant effects when applied locally.

In frogs fibrillary contractions and convulsions are observed, followed by weakness and paralysis of the spinal cord. Hæmorrhages have also been found in the stomach when the drug was injected into a lymph-sac.

Benzoic acid (C_6H_5COOH) combines with glycocoll in the body to form hippuric acid ($C_6H_5CO—NHCH_2COOH$), which is excreted in the urine. Some of the benzoic acid escapes in the urine unchanged, however, the proportion of hippuric acid formed apparently varying with the general health and the condition of the kidneys, and also with the dose administered. After large doses a reducing body has been observed in the urine, presumably glycuronic acid. Traces of benzoic acid are found in the saliva of the dog after its administration, but it does not seem to be excreted here in man. In birds benzoic acid is excreted by the kidneys as ornithuric acid ($C_{19}H_{20}N_2O_4$), from which benzoic acid can be split off, leaving ornithin. Benzoic acid often increases the nitrogen eliminated in the urine, so that in these cases it augments the decomposition of the proteids like salicylic acid; in other investigations no material change has been observed, probably because the benzoic acid was changed too rapidly to hippuric acid to admit of its action on the metabolism being developed. It differs from salicylic acid in reducing the uric acid excretion. Some diuresis occurs after benzoic acid.

Cinnamic acid ($C_6H_5—CH{=}CH—COOH$) seems to resemble benzoic acid in its pharmacological characters, but has not been so carefully examined. It increases the leucocytes of the blood and the uric acid of the urine to a marked degree.

Preparations.

Acidum Benzoicum (U. S. P., B. P.) (C_6H_5COOH), benzoic acid or flowers or benzoin, is prepared from benzoin by sublimation, or from toluol, and consists of white, feathery crystals, almost odorless, with a warm acid taste, very insoluble in water, soluble in alcohol, ether, fixed and volatile oils and in alkaline solutions. 0.3–1 G. (5–15 grs.), in powder or pill.

Trochiscus Acidi Benzoici (B. P.), each contains ½ gr.

Sodii Benzoas (U. S. P., B. P.), easily soluble in water. 0.3–2 G. (5–30 grs.), in solution.

Ammonii Benzoas (U. S. P., B. P.), 0.3–2 G. (5–30 grs.).

Benzoic acid is also contained in paregoric.

The **Balsams** are mixtures of resin, volatile oils, benzoic and cinnamic acids and their esters and small quantities of other aromatic bodies.

Benzoinum (U. S. P., B. P.), benzoin, a balsam obtained from Styrax Benzoin and probably from other species, varies in its composition with its place of origin, but contains much less cinnamic acid than the other balsams.

Styrax (U. S. P.), or storax, a balsam prepared from the inner bark of Liquidambar orientalis, contains resins, cinnamic acid and its esters.

Tinctura Benzoini (U. S. P.), 1 c.c. (15 mins.).

Tinctura Benzoini Composita (U. S. P., B. P.) contains, in addition to benzoin, storax, aloes and balsam of Tolu, and was formerly known as Balsamum Traumaticum. A number of old remedies resembled it in composition, such as Friar's balsam, Turlington's balsam, Jesuits' drops, etc. 2–8 c.c. (30 mins.–2 fl. drs.).

Balsamum Peruvianum (U. S. P., B. P.), Balsam of Peru, a balsam obtained from Toluifera Pereiræ (U. S. P.), or Myroxylon Pereiræ (B. P.), contains cinnamic and benzoic acids (traces) and their esters, and resins. Applied externally, either alone or in alcoholic solution. 1 c.c. (15 mins.).

Balsamum Tolutanum (U. S. P., B. P.), Balsam of Tolu, a balsam obtained from Toluifera Balsamum or Myroxylon Toluifera, resembles balsam of Peru in composition, but contains more benzoic acid. 0.3–1 G. (5–15 grs.).

Syrupus Tolutanus (U. S. P., B. P.), 4–16 c.c. (1–4 fl. drs.).

Tinctura Tolutana (U. S. P., B. P.), 1–4 c.c. (15–60 mins.).

Therapeutic Uses.—Benzoic acid and its sodium salt have been suggested as antiseptics and seem to be quite as satisfactory as salicylic acid, but have never been widely employed. Benzoin and the balsam of Peru are used extensively in parasitic skin diseases, especially in scabies. Internally the benzoates have been employed as substitutes for salicylic acid in acute rheumatism, but have not proved efficient. Sodium benzoate has been administered as an intestinal disinfectant and as an antiseptic and slight irritant in diseases of the genito-urinary tract, such as cystitis and gonorrhœa. It was formerly supposed that benzoic acid lessened the uric acid excretion and dissolved the uric acid deposits in the bladder and tissues by forming hippuric acid, but this is now recognized to be erroneous, and the treatment of gout and other diseases based on this theory may be considered obsolete. Lithium benzoate is a survival of this treatment, lithium being credited with special solvent properties.

Benzoic acid is still used as an ingredient in expectorant mixtures, in which, however, it is generally prescribed as the simple or compound tincture of benzoin, or as one of the Tolu preparations. It is said to be beneficial in cases in which the mucus is tenacious and is coughed up with difficulty. The syrup of Tolu may be regarded simply as a flavoring ingredient, for it contains too little of the balsam to have any other effect.

Balsam of Peru and pure cinnamic acid have been administered by hypodermic and intravenous injection and by the mouth in pulmonary tuberculosis, in the belief that they would induce irritation, inflammation and subsequent cicatrization of the tubercular nodules, but there is no reason to suppose that they have any such effect, and the treatment has never advanced beyond the experimental stage.

When the balsams are administered in large quantities, the addition of an acid to the urine is followed by the formation of an abundant precipitate in some cases, and this has given rise to the belief that they tend to irritate the kidneys. The precipitate appears to be not albumin but the resin in most cases, however, for it is dissolved by the addition of alcohol.

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Nitrobenzol Compounds.

The nitrobenzol bodies are chiefly of interest because they have often given rise to poisoning of late years from their extensive use in chemical manufactures and to flavor alcoholic liquors. They are readily absorbed from the skin and serious symptoms have followed the wearing of clothing dyed with them. In man nitrobenzol causes a grayish-blue, cyanotic color of the skin and visible mucous membranes, often with nausea, vomiting, great muscular weakness, marked dyspnœa, delirium and some convulsive movements of the face and jaws, less frequently of the whole body. Total unconsciousness and coma are followed by arrest of the respiration.

These effects are due in part to changes in the blood, in part to central nervous action, in which stimulation and paralysis seem to follow one another. The blood is found of a chocolate-brown color, and some of the red cells are either deformed or entirely destroyed. Examined with the spectroscope, methæmoglobin is very often found in it, while in other cases an absorption line is observed between the yellow and the red, which does not seem to correspond to that of any of the ordinary hæmoglobin products, and has therefore been called the nitrobenzol-hæmoglobin line. The blood contains a much smaller amount of oxygen than normally, in some cases only one per cent. instead of seventeen, and artificial respiration or even shaking the blood in air fails to oxidize it further, as the combination of nitrobenzol and hæmoglobin seems to be incapable of absorbing oxygen. Similar changes may be produced in venous blood outside the body by shaking it with nitrobenzol. These changes in the blood are the cause of the cyanosis, and the imperfect oxidation of the tissues leads to the appearance of a number of abnormal products in the urine, such as hæmatoporphyrin. In animals a gastrointestinal catarrh is almost constantly produced unless the intoxication is very acute, and this occurs even when the poison is inhaled or injected subcutaneously.

Metadinitrobenzol ($C_6H_4(NO_2)_2$) has repeatedly given rise to poisoning in the manufacture of the modern explosives, such as roburite and securite. In action it resembles nitrobenzol, but is more poisonous, and the gastric symptoms are more marked. Amblyopia and a jaundice-like coloration of the skin often occur from prolonged exposure to this poison.

Picric Acid ($C_6H_2OH(NO_2)_3$) is an irritant to the skin and mucous membranes, and in large doses causes vomiting and often anuria and strangury. A characteristic symptom is the yellow, icteric color of the skin and mucous membranes, which is due, not to true jaundice, but to the staining of the epithelium by the acid. It produces this coloration when taken internally, and itching is often complained of, and some eczema or erythema has been observed. Violent convulsions occur sometimes, in other cases collapse. The urine is yellow or red, and contains some casts but little or no albumin, and no bile, the absence of the last serving to diagnose the intoxication from jaundice. Picric acid tends to destroy the red cells of the blood in animals, but no marked diminution of these has been observed in man. It is excreted as picramic acid ($C_6H_2OH{\cdot}NH_2(NO_2)_2$) in the urine.

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Naphthylamine.

Stern has observed a curious and almost unique series of symptoms after the administration of several hydrated derivatives of β-naphthylamine to mammals. The most interesting of these were dilatation of the pupil and protrusion of the eyeball, and a very marked rise in the temperature amounting in some cases to 4½° C. The dilatation of the pupil, which was not observed in the later experiments of Fawcett and White, is ascribed by Stern partly to local action on the dilator fibres or the terminations of the sympathetic nerves in the iris, but mainly to some central stimulation. The rise of temperature is produced in part by the output of heat being lessened through contraction of the cutaneous vessels, in part by increased oxidation in the tissues and augmented heat production. The contraction of the vessels is to be attributed chiefly to stimulation of the vaso-motor centres, although the drug seems to have some direct effect on the muscular walls of the vessels also. Cocaine has a somewhat similar but weaker action, but the naphthylamine compounds do not produce local anæsthesia.

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Toluylendiamine.

Toluylendiamine ($C_6H_3CH_3(NH_2)_2$) has never been used in therapeutics, but it is of importance from the light which it has thrown on some forms of jaundice. Stadelmann found that its administration in dogs produced the typical symptoms of icterus, while in cats the icterus was less marked, but very large quantities of hæmoglobin were excreted in the urine. The explanation of this action is the destruction of the red cells in the blood, which leads in the dog to the formation of large amounts of bile pigments in the liver. Some of this pigment is reabsorbed from the bile vessels and leads to typical jaundice. The absorption is promoted by a curious increase in the mucus secretion of the bile ducts, which renders the bile more viscous, and by thus delaying its evacuation into the intestine favors its absorption into the blood. This increased mucus formation is believed to be due to the action of the poison on the secretory cells of the larger bile ducts. The formation of bile pigment from hæmoglobin liberates large quantities of iron, which seems to be stored in the liver, spleen and bone marrow. In the cat the hæmoglobin is not so largely formed into bile pigment, but escapes in the urine. In both animals some methæmoglobin is probably formed.[1]

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Benzol.

Benzol, or benzene, is much less poisonous than its hydroxyl compounds, but may give rise to symptoms resembling those of phenol when it is inhaled in large quantities. It was at one time suggested as a general anæsthetic, but the preliminary excitement is very much greater than that seen in the use of chloroform or ether, and partakes much more of a convulsive character. Even after unconsciousness and anæsthesia is attained, the characteristic muscular tremor of the aromatic compounds continues. In some animals it produces violent and prolonged convulsions, with only partial loss of sensation, and even large quantities do not cause the complete relaxation of the muscles requisite for surgical operation. It seems to have little or no irritant action on the alimentary canal or kidneys in animals, and is excreted in part by the kidneys as phenol double sulphate, in part unchanged by the lungs.

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[1] A somewhat similar action follows the administration of *Cephalanthin*, the active principle of Cephalanthus occidentalis, Button-bush or Swamp dogwood (Mohrberg).

Santesson states that hæmorrhages occur very frequently in fatal poisoning in man, and found the same result in experiments on rabbits; he ascribes it to fatty degeneration of the arterial walls, which was well-marked in most of his experiments. A number of cases of fatal intoxication are on record, some of them arising from the drug being swallowed by suicides, but most of them from the accidental inhalation of large quantities in india-rubber factories. Animals exposed to benzol vapor do not seem to absorb enough to be seriously poisoned, but when it is injected subcutaneously or applied over a large skin area, it proves fatal to them. The benzol of the B. P. contains toluene and is used only for pharmaceutical purposes.

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Pyoctanine.

Several of the dyes derived from aniline are used to stain pathogenic germs and to differentiate them from each other. This suggested to Penzoldt the idea that these bodies, having a distinctly greater affinity for the microörganisms than for the tissues surrounding them, might be used as antiseptics or disinfectants, and Stilling introduced several of them into therapeutic use under the name of pyoctanines. Some of these dyes have been found to have a certain antiseptic action, but the hopes that were formerly entertained as to their specific action have proved delusive, and their use in medicine (chromotherapeutics) is now very limited, and promises to fall into oblivion.

Methylthioninæ Hydrochloridum (U. S. P.), methylene blue, a dark green powder, readily soluble in water and alcohol, forming a deep blue solution. Dose, 0.25 G. (4 grs.).

XXX. FORMALDEHYDE.

It has recently been shown by numerous investigators that formaldehyde (HCOH), the aldehyde derived from the oxidation of methyl alcohol, is a very powerful germicide, while it is not very dangerous to the higher animals. The aldehyde is a colorless gas and has been used either in solution in water (*formaline*) or as a vapor. As a germicide it is estimated to be equally efficient with corrosive sublimate, and its volatility enables it to penetrate much more rapidly, so that it may be used for purposes for which the latter is unsuitable. On the other hand, its volatility and irritant action preclude its use as an antiseptic to prevent the growth of microbes in wounds.

Action.—The vapor is very irritant when inhaled, causing stinging and prickling in the nose and throat, salivation and tears, and bronchial irritation and catarrh. In the few cases of poisoning in man recorded the symptoms were those of gastric irritation and consequent collapse. When swallowed by animals the watery solution produces nausea and vomiting, which are followed by narcosis, coma, and in the rabbit by convulsions and opisthotonos. The respiration in the dog is very greatly accelerated some time before death, while in the rabbit this is not so marked or is entirely absent. The blood-pressure is increased at first and the heart is slow, presumably from direct or indirect stimulation of the medullary centres. The formaldehyde absorbed undergoes complete oxidation in the tissues and none of it reappears in the excretions. The symptoms induced in animals by formaldehyde are for the most part due to the intense local irritation and inflammation, but in addition a specific destructive effect has been observed in the liver and kidney (Fischer). In the blood it induces alteration in the form of the red cells and hæmatin appears.

The powerful action of formaldehyde on microbes and on mucous membranes is believed by Loew to be due to its combining with the amino groups in the proteins, and as a matter of fact, a number of changes have been described in the reaction of proteins exposed to formaline. For example, egg albumin and serum to which formaldehyde solution has been added are not precipitated by heat and are less easily digested by ferments, while casein is not coagulated by the rennet ferment. Some of the ferments (pepsin and diastase) are not affected by small amounts of formaldehyde, while trypsin and papain lose their activity wholly or in part.

PREPARATIONS.

LIQUOR FORMALDEHYDI (U. S. P.), formalin, a solution of formaldehyde in water containing not less than 37 per cent. of the gas, which may be obtained from it by distillation.

Paraform, a solid polymer of formaldehyde, which is decomposed by heat and liberates the formaldehyde in gaseous form.

Some formaldehyde may be formed by the incomplete combustion of methyl alcohol, and several lamps have been devised with this object in view, but have not proved satisfactory.

Uses.—Formaldehyde is too irritant to admit of its use as an antiseptic in medicine and surgery, but it has been largely employed to disinfect instruments, furniture, clothes and rooms, which cannot be sterilized by heat. Diluted formaline (4 per cent.) may be used for some of these purposes, or the vapor may be disengaged by distillation from formaline or by heating paraform. Large rooms filled with formaline vapor and left for some hours are found to be almost completely sterilized, so that cultures of the pathogenic microbes exposed in them cease to grow even when removed from the atmosphere. Novy makes the room to be disinfected as nearly air-tight as possible and distils the formaldehyde into it through the key-hole of the door. He states that the gas disengaged from 150 c.c. (5 oz.) of 40 per cent. formaline is sufficient for each 1000 cubic feet of space, if the room be closed for 10 hours. The odor of formaline may then be removed by sprinkling ammonia solution with which it forms a solid combination. Formaldehyde not only destroys the microbes, but also alters the toxins formed by them so that they are no longer poisonous, even in very large quantities.

Formaldehyde has frequently been added to food, especially to milk, as a preservative. Tunnicliffe and Rosenheim found that added to milk in the proportion of one to five thousand, formaldehyde did not seem to be deleterious to healthy children, but in the case of a weakly child the proteid waste was increased, and it is certainly not to be regarded as a harmless method of preserving food.

Formaldehyde is not alone in its germicidal action, although it is much more powerful than the other less volatile and less active aldehydes, such as acetaldehyde.

Urotropine.

Urotropine, or hexamethylenamine ($(CH_2)_6N_4$), has no important action itself, but is of interest from its liberating formaldehyde in the course of its excretion in the urine; the formaldehyde thus formed acts as a disinfectant or antiseptic in the urinary passages. It seems superior to any other urinary antiseptic, microbes in the urine decreasing in number or sometimes disappearing altogether within a few hours of its administration. Formaldehyde also appears in the bile and pancreatic juice, when urotropine has been administered, and this has suggested its use in gall-bladder infections. No symptoms arise from ordinary doses of urotropine, but large quantities have occasionally given rise to pain and discomfort in the bladder, and more rarely to hæmaturia. Formaldehyde forms some soluble combinations with uric acid, and this suggested the use of urotropine in gravel, calculus, gout, and similar conditions, but the results have been disappointing.

HEXAMETHYLENAMINA (U. S. P.), UROTROPINE ($(CH_2)_6N_4$), is a white crystalline powder, very soluble in water. Dose, 0.2–0.6 G. (3–10 grs.), to be taken in a glass of water.

Urotropine is used in cystitis and urethritis and to destroy typhoid bacilli in cases in which they are eliminated by the kidney. It may also be given as a prophylactic before a catheter is passed.

Numerous compounds of urotropine have been introduced of late years by rival manufacturers, but none of these has proved equal to the original drug.

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Change in physical properties of fluids. Salt action.

PART III.

COMBINATIONS OF THE ALKALIES, ALKALINE EARTHS, ACIDS AND ALLIED BODIES.

SALT-ACTION.

THE action of most of the substances discussed in the foregoing pages may be best explained by supposing that they cause some change in the living matter of one or more organs through some specific affinity for it. Thus strychnine may be supposed to act on the spinal cord by forming some loose combination with the protoplasm of the nerve cells, while prussic acid changes protoplasm generally, through a similar affinity for it.

Some bodies, on the other hand, seem to have little specific affinity for living matter, but affect it largely as they do dead colloid substances, through changing the physical properties of the fluids contained in it or surrounding it. This action is seen best in the effects of some of the salts of the alkalies, and is therefore known as "salt-action," although it is not confined to these, but is shared by any soluble, diffusible body which can circulate in the tissues in sufficient quantity. The salts of strychnine or of prussic acid are undoubtedly capable of inducing physical changes similar to those observed after chloride of sodium, but they play no part in the symptoms induced by these poisons, because animals die from the specific action long before the quantity necessary to induce the "salt-action" can be absorbed. In the case of less poisonous organic substances, such as sugar and urea, however, many of the features of salt-action may be observed.

Much light has been thrown on the nature of salt-action by the recent advances in physical chemistry, which have shown that many of the changes in the animal body are analogous to those observed in the chemical laboratory. When an aqueous solution of sugar or salt is carefully poured on distilled water, so that two layers are formed, a process of **Diffusion** commences, the dissolved molecules passing throughout the fluid until the whole becomes homogeneous, each cubic centimetre containing an equal number of molecules of sugar or salt. If instead of distilled water, a solution of another salt be used, the same process results, the two bodies diffusing throughout both fluids until these become homogeneous; and if the fluids be separated by a membrane which offers no obstacle to the penetration of the water and salts, a similar interchange occurs. When a membrane is used which does not allow the salt to pass through it, a different result is observed; if it separates salt solution from pure water, the latter passes through

Osmotic pressure is the strength with which a substance attracts water to it or with which it holds water in which it is dissolved from diffusing out. Cell has specific affinities for salts

until it is exhausted, or until some factor such as hydrostatic pressure puts a limit to further movement. This is readily intelligible, for the pure water can pass without hindrance towards the salt, but having rendered the solution more dilute, it cannot diffuse in the opposite direction, because this would be equivalent to forming a more concentrated solution of the salt, and this requires the expenditure of energy, such as heat, while in the case in point there is no energy available for this purpose. A similar result is obtained if the membrane separate solutions of a non-permeating and of a permeating salt, the latter passing through with the fluid in which it is dissolved until some extraneous factor counterbalances the diffusion.

The resistance offered by a non-permeating salt to the passage through the membrane of the fluid in which it is dissolved is known as the **Osmotic Pressure** of the solution and varies with the number of molecules and ions (see page 486). When both the salts in solution on the opposite sides of the membrane are unable to penetrate through it, the movement of the fluid is determined by the relative osmotic pressure on the two sides, water tending to pass from the solution with the lower osmotic pressure (the *hypotonic* solution) to that with the higher (*hypertonic*) until an equilibrium is established by the osmotic pressure becoming equal on the two sides, when the solutions are said to be *isotonic*. As a general rule, however, membranes are partially permeable to both salts, and the movement of the fluid is determined by the relative osmotic pressure of the fluids divided by the rate at which the salts pass through the membrane. If sufficient time is allowed to elapse, the two solutions will become identical in composition, but during a short period the details of the process are difficult to follow, and the complexity is infinitely greater when instead of a single salt on each side of the membrane there are several salts, each differing in its permeability and concentration. The direction of the flow is thus determined by the sum of the osmotic pressure on each side divided by the penetrating power of each individual substance.

In the animal body such membranes as are used in physical experiments are not met with, but the cells consist of colloid substances containing fluid and diffusible bodies, and are surrounded by liquids which are practically salt solutions isotonic with the contents of the cells; any change in the contents of a cell or in the lymph surrounding it must of necessity give rise to a certain movement of the fluids in the same way as if each cell were surrounded by a membrane. All the cells of the body are permeable by water, and a dilution of the fluids surrounding them is therefore followed by an increase in their fluid contents and swelling. On the other hand, some salts seem to diffuse into cells practically without resistance, while others fail altogether to do so, or penetrate only very slowly. The subject has been investigated with most care in the red blood cells, which are found to be penetrated by ammonium chloride and some other salts, while they are impermeable by sodium chloride and the other salts of the fixed alkalies. Accordingly, when the red blood cells are surrounded by a solution of ammonium chloride, whatever its concentration, their fluid contents are increased; they swell up and eventually lose their hæmoglobin, exactly as if they had been placed in pure water. When they are placed in an isotonic solution of chloride of sodium,[1] they remain unchanged in size, while in a hypertonic solution their fluid diffuses out, and they shrink; a hypotonic solution acts like pure water, the osmotic pressure of the salts in the corpuscles overcoming the smaller osmotic pressure of the surrounding fluid. The behavior of a cell towards salts therefore varies with each individual salt. Solutions of those by which it is perfectly permeable have the same effects as pure water; but the less diffusible the salt, the more tendency it has to prevent the entrance of the water in which it is dissolved, and if in sufficient concentration, to withdraw fluid from the cell. A perfectly diffusible substance can never prevent the entrance of fluid, however concentrated be its solution.

All the cells of the body do not resemble each other in their permeability, nor in the salts which diffuse into them. For example, the intestinal epithelium takes up some of the salts of the alkalies, while the red blood cells do not.

An even more obscure relation between the salts and colloids has been discovered by Hofmeister, who found that gelatin plates thrown into weak salt solutions absorb more fluid than when they are put in distilled water, and who inferred from this that colloid substances have a special affinity for salts quite apart from their permeability by water, and that they are not merely passively permeated by salt solutions, but have an active attraction for some of the salts contained in them. This affinity, which may depend on the same factor as the permeability of the cell, varies for different salts.

The rôle played by the physical forces in the salt-action is thus determined not only by the physical properties of the fluids, but also by the "affinity" of the cell contents for certain of the constituents of these fluids. In conclusion it may be stated that these physical forces are not sufficient to explain the whole processes of absorption and excretion, as has sometimes been stated; the physical forces merely influence the processes of nutrition, which depend on forces hitherto unexplained and possibly exercised only by the living protoplasm.

The penetrating power of salts seems to be connected with the property which many of them possess of precipitating certain colloid substances from their solutions in water, for those salts which permeate gelatin plates are found to precipitate colloids less than others. Thus the sulphates of the alkalies, which permeate gelatin plates with difficulty, throw globulins out of solution much more readily than the chlorides. Here again, however, different colloids vary in their affinities, some reacting to one sulphate and not to another. This reaction is not confined to the proteins but extends to many other colloid substances.

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[1] An isotonic solution is here used to indicate a solution in which the osmotic pressure is equal to that of the blood serum, and (presumably) to that of the contents of the red blood cells.

S. of chem dissociated into ions. each having same osmotic pressure as the whole molecule. The ions have the phar. action. Ions are + n - charged.

In the dilute solutions found in the tissues, the salts do not exist as such, but are largely dissociated into two or more **Ions** charged with positive and negative electricity. Thus if a small quantity of potassic chloride be dissolved in water, it is dissociated into a positive K ion (Kation) and a negative Cl ion (Anion).[1] Similarly sodium sulphate dissolved in water exists as two Na ions and a negative SO_4 ion. One effect of this is that the osmotic pressure of such a dilute solution diverges considerably from what might be expected if it were calculated from the number of molecules present, because each of the ions exerts the same osmotic pressure as a whole molecule. But a more important fact is that the ions of a salt, and not the whole molecule, form chemical combinations, and thus exert their pharmacological action. Thus what is known as the action of many poisons is really the action, not of the molecule as a whole, but of one of the ions. For example, cyanide of potassium is said to possess a very poisonous action, but this is due not to the molecule KCN as such, but to the CN ion, which forms from it in solution. When ferrocyanide of potassium is dissolved, on the other hand, no CN ion is formed, the salt dissociating into the K and $Fe(CN)_6$ ions, and ferrocyanide of potash is therefore entirely devoid of the cyanide action. In the same way the corrosive effects of potassium or sodium hydrate are not due to the potassium or sodium, but to the hydroxyl ions (HO), for the same K or Na ions are obtained when KCl or NaCl is dissolved, but neither of these is corrosive. Thus when a dissociable body is administered, not one, but two, separate agents are put in action in the tissues, and in describing the effects of one of these dissociable bodies, the effects of each ion have to be taken into consideration. In the organic materia medica, many such substances occur, but in the great majority of them the action of one ion is so much more powerful than that of the other that the less important one may be neglected. Thus, morphine sulphate in the body exists as a morphine and a sulphate ion, but the action of morphine is so much the more powerful that the sulphate ion may be left out of account. This is shown by the fact that morphine hydrochloride, which is dissociated into morphine and chloride ions, has practically the same action as morphine sulphate. In the same way the positive ion (Na, K, etc.) of the cyanides may be neglected, because the negative CN ion is so poisonous that the positive ion can never be present in the tissues in sufficient quantity to elicit any action.

When, however, less poisonous substances are involved, the case is quite different. Thus, although the hydrobromide and the sulphate of morphine may be described as possessing the same action, because the morphine ion alone is taken into account, the sulphate and bro-

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[1] These ions are not to be confused with atoms of potassium and chlorine, for they possess none of the chemical properties of these elements; the physical difference consists in each ion being charged with a burden of electricity, positive or negative.

Bromated Camphor not dissociated so must not effect Br action. Alcohol not dissociated but acts as mol. yet KOH acts via OH ion

mide of potassium induce quite different symptoms,[1] because here larger quantities can be administered, and the SO_4 and Br ions are present in sufficient quantities to elicit their specific action, which is quite as important as that of the K ion.

In this connection it is to be noted that many bodies are not dissociated. For example, potash, KHO, and alcohol, C_2H_5HO, both contain HO, but in the former the hydroxyl is dissociated in water, while the latter remains undissociated. Thus, when KHO comes in contact with a mucous membrane, the molecule does not act as such, but the effects are due to the HO ion, and to a less extent to the K ion. On the other hand, alcohol acts as a molecule, and the caustic effects of the HO ion are not observed under it. A similar contrast is offered by the effects of the dissociable KBr and bromated camphor, which is not dissociable but acts as an entire molecule. It is therefore vain to expect the bromide action from this compound, for the bromides act from the presence of the bromide ion, which is not formed from monobromated camphor.

This renders the classification of the inorganic salts a matter of some difficulty, for it is necessary to consider the action of each ion alone, and then to find how far its effects are modified by the presence of the other ion with which it is associated in the molecule. It is obviously illogical to consider under a "potassium series" all the salts of potash, for in many of these the K ion is of no importance, while in others it is the chief factor.

The effects of an ion cannot be determined except by administering it along with another in the form of a salt, but certain ions are so inactive in the tissues that if any effect is noted after a compound of which they form part, the action can be ascribed with certainty to the other ion, unless the change arises from alteration of the physical properties of the fluids. For example, the sodium ion (Na) and the chloride ion (Cl) are both practically inert, except in so far as they change the osmotic pressure. Thus, if a sodium salt or a chloride be found to cause some change which is not due to the physical alteration, the action is attributed to the other ion of the molecule. Before entering on the study of the action on the ions, however, it is obviously necessary to learn the symptoms caused by alteration of the physical properties of the fluids, and this can best be done by examining the effects of bodies which act only in this way, namely, chloride of sodium and water.

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[1] Even at the present day it is sometimes a matter of discussion whether the bases or the acids are the determining factors in the action of the salts of the alkalies. The question depends entirely upon which salts are compared. If chloride of sodium and chloride of potassium be compared, the determining factor is the base, but if a chloride and a cyanide be in question, the base with which they are combined is practically of no importance.

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I. SODIUM CHLORIDE AND WATER.

The most typical example of salt-action is presented by chloride of sodium, for this salt is always present in large quantities in the body, and has practically no specific action; the sodium and chloride ions are ordinary and necessary constituents of the fluids of the body. The action of this salt is therefore limited to the alteration in the physical properties of the fluids, which its presence in excess or in limited amount induces. In the same way the action of water is due only to its diluting the body fluids and lessening their osmotic pressure, and it may therefore be described along with that of salt.

Most of the tissues hitherto examined in regard to this point have proved permeable by both the Na and the Cl ions, but in every case there is a certain amount of resistance offered so that the presence of salt in the fluid round a cell always prevents its free diffusion into the interior; *i. e.,* sodium chloride solution exerts osmotic pressure on the cell. The molecular weight of common salt being small, the osmotic changes induced by it are greater than those induced by an equal weight of most other salts, because a larger number of molecules exist in each gramme. It also dissociates into its two ions more readily than many others, and this lends it still greater osmotic power.

A common example of the osmotic action of salt is seen in its use to preserve meats from putrefaction, which it accomplishes by withdrawing the fluids of the meat, and thus rendering it dry and hard and unsuitable for the growth of microbes.

In the same way the **Red Blood Corpuscles** shrink in size when they are placed in a solution of salt which is stronger than the blood-plasma (hypertonic), because the water is withdrawn from them. In dilute (hypotonic) solution, on the other hand, or in water, they swell up because they absorb water, while in solutions of the same osmotic pressure as the plasma (isotonic) they remain unaltered in size. When water is absorbed into the corpuscles, some obscure change takes place in them, and the hæmoglobin diffuses into the surrounding liquid.

Muscle is affected in a similar way, strong salt solutions withdrawing fluid from it, while weaker ones are absorbed, and both tend to destroy its vitality in a longer or shorter time. In isotonic salt solution, on the other hand, muscle preserves its irritability for many hours. Strong salt solutions irritate exposed **Nerves** from the withdrawal of their fluid contents, and on the other hand, distilled water is equally fatal to them.

These changes are undoubtedly due to the imperfect permeability of the cells by the sodium and chloride ions, and as regards the red blood corpuscles, it is definitely known that salt penetrates them with the greatest difficulty, if at all, and the changes induced in them by solutions of different concentration and by water are due to the alteration of their fluid contents only. If this were true for all cells, the isotonic solution would preserve them in a normal condition until they slowly perished for want of oxygen and from exhaustion of their reserve of food. But this is found not to be the case, for muscle suspended in isotonic solution often develops a more or less rhythmical series of contractions, while the frog's heart ceases to beat after a time when it is perfused with isotonic salt solution, although it has not exhausted its energy entirely. Similarly some ova and fish living in sea water die if they are put in a solution of sodium chloride isotonic with sea water while they live much longer in distilled water. It is obvious that in these instances no change in the distribution of the fluids can occur, for the osmotic pressure of the fluid is unchanged. In other words the death of these animals in pure salt solution is due, not to the physical action of the salt (salt action), but to the sodium ion exercising a deleterious effect on them. This deleterious action may be neutralized by the addition of traces of salts of calcium or of some other bivalent elements, while the monovalent kations have less antagonistic effects (Loeb). In the natural environment of living cells both sodium and calcium are present, so that the toxic effect of sodium (see Calcium) can scarcely be observed except when small masses of tissue are thoroughly washed with salt solution; as far as the higher animals are concerned, then, salt may be regarded as indifferent in itself and as acting only through changing the distribution of the fluids. And as isotonic solutions have no osmotic action, they are entirely inert.

Water or very dilute salt solutions penetrate into the superficial cells of the **Skin**, which therefore become swollen and softened. Concentrated solutions, on the other hand, rather tend to draw fluid from the surface cells, and this along with the passage of salt into them, causes some mild irritation. Neither salt nor water is absorbed into the circulation through the skin in mammals. A much greater absorption into the superficial tissues occurs on less protected parts, such as the cornea, which becomes white and clouded when strong salt solutions are applied to it. Similarly, either pure water or strong salt solution causes considerable pain and smarting in the nasal passages, or in wounds, from the disturbance of the normal relation of salt and fluid in the surface cells. Isotonic solutions, on the other hand, cause no pain.

In the **Mouth** salt has a characteristic taste, and strong solutions act as astringents here and in the throat. In the **Stomach** its action is very much like that on other mucous membranes, hypotonic solutions causing swelling, while hypertonic solutions cause a withdrawal of fluid and a shrinking of the cells. This withdrawal of fluid and imbibition of salt may set up such irritation as to induce vomiting.

The digestion in the stomach does not always seem to be improved by salt in the food, for even small quantities have been found to lessen the acidity of the gastric juice, and the amount of albuminous food absorbed from the alimentary canal in animals is but little altered when salt is added to the food. It is very possible, however, that a small quantity of salt in the food renders it more palatable in many instances, and thus increases the reflex flow of the gastric juice. (Compare Simple Bitters.) Dapper finds that the hydrochloric acid of the stomach is increased in some persons and diminished in others by mineral waters containing common salt as their chief ingredient. These waters have no effect on the secretion directly, then, but may alter it by changing the nutrition of the gastric mucous membrane, or by arousing secretion reflexly by their taste.

Salt solutions are **Absorbed** little in the stomach, largely in the bowel, but considerable difference of opinion exists as to the means by which this is accomplished. An attempt has been made to explain absorption by the action of the known physical processes, such as diffusion, osmosis and filtration, but these seem quite inadequate without the assumption that there is a constant tendency for fluids and for some salts to pass inwards from the lumen of the bowel. This tendency may be opposed or strengthened by the osmotic pressure. Thus hypotonic solutions and water are absorbed rapidly, because here not only is the natural flow inwards, but the osmotic current is in the same direction, the fluid being of lower osmotic pressure than the blood serum. In solutions of equal osmotic pressure with the blood serum the absorption is slower, because here the natural flow alone is active, while hypertonic solutions are still more slowly absorbed or may even be increased at first, because the osmotic pressure acts in the opposite direction from the natural flow. Accordingly, while hypotonic and isotonic solutions disappear rapidly, the absorption of the stronger solutions may be preceded by a period in which the fluid of the bowel actually increases, water diffusing into it from the blood. At the same time the salt is being absorbed and the solution eventually becomes isotonic and is absorbed. The absorption from the bowel is very similar to that described by Hofmeister in gelatine plates, and it is possible that the unexplained tendency for fluids to pass inwards may be due to some "affinity" between the salts and the colloids of the bowel wall.

The **Blood** and **Lymph** are in turn affected by these processes. When hypotonic solutions pass into the blood from the bowel, the proportion of solids and liquid is of course changed and fewer corpuscles and less solid matter are found in the cubic millimetre than normally (hydræmia). On the other hand, when strong salt solutions in the bowel cause the effusion of fluid, the blood becomes more concentrated than in ordinary conditions. After the reabsorption of the fluid, the normal balance of plasma and corpuscles must be restored, and to effect this currents are set up between the blood and the fluid of the surrounding lymph. These currents have been investigated by the injection of salt solutions directly into the blood, and not by their absorption from the bowel, but the processes probably resemble each other in their chief features. When the blood is rendered hypertonic by the injection of strong salt solution, the lymph at once begins to pour into the blood vessels by osmotic attraction and this leads to hydræmia and increased capillary pressure, the arterial tension remaining unchanged. This augmentation of the capillary pressure in turn induces a flow of lymph from the blood vessels into the lymph spaces.

The flow of lymph from the blood vessels is first, therefore, diminished in amount by the presence of salt in the intestine and blood and then increased again by the high capillary pressure. This interchange between the blood and lymph is continued, because as the salt is excreted by the kidneys and other excretory glands, a continual variation in the osmotic pressure of both blood and lymph occurs.

The details of the changes between the blood and lymph under the action of salt and water are still obscure, but there is no question that the absorption of either of these leads to an augmentation of the normal exchange of these fluids. In particular, it is still undecided whether the cells of the vessels possess a secretory function similar to that of the secretory glands, or whether the whole process may be attributed to variations of osmotic pressure and filtration.

The changes in the blood and lymph are followed by an increased activity of the **Excretory Organs.** Thus the urine[1] is much augmented by the injection of salt solution into the blood, less so by the absorption of water or salt solution from the stomach and bowel. A good deal of discussion has been carried on in recent years as to the cause of the diuresis from salts and water, and some authorities hold that the presence of salt in excess in the blood stimulates the renal cells much in the same way as caffeine. But a more plausible explanation is that the greater volume of the blood, following the absorption of the fluid and the increased flow of lymph, results in an increase in the capillary pressure in the glomerulus and this in turn promotes the escape of fluid into the capsule. A more rapid flow through the tubules follows, and the glomerular secretion lies in them for a shorter time, so that there is less tendency for its constituents to be reabsorbed into the blood vessels; the fluid reaching the ureters is accordingly increased, and the dissolved salts and urea are also augmented; those constituents which in ordinary circumstances are absorbed most readily by the epithelium of the tubules are increased more than the others, so that the chlorides and the potassium and sodium of the urine rise much more than the urea, phosphates or sulphates, even when the diuresis is due to the absorption of water. Any other diffusible body increases the urine in the same way as salt, and urea has therefore been suggested as a diuretic; it differs from salt in the difficulty with which it is absorbed from the tubules of the kidney and this further retards the absorption of the fluid, so that urea may probably have a more powerful diuretic action than sodium chloride.

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[1] The following explanation of the diuresis is based upon the theory that all the constituents of the urine are excreted by the glomerulus, and that some of them, notably much of the fluid and the alkali chlorides, are reabsorbed in passing through the tubules. See Journ. of Physiol., xxvii., p. 429; xxviii., p. 431.

Other secretions, such as the saliva, are increased by salt, and this not only by a reflex from the mouth, but also because some of the salt is excreted by the salivary glands.

When very large amounts of isotonic salt solution are thrown into the blood, the organism may have difficulty in excreting it rapidly enough, and the tissues are therefore found to be swollen and œdematous in some parts of the body.

When salt solution is injected into the serous cavities or into the lymph spaces, absorption occurs in the same way as from the alimentary canal, except that in the case of the serous cavities osmosis seems to play a greater, and the other forces a smaller rôle, than in the stomach and intestine.

The administration of large quantities of fluid, either as water or as dilute salt solution, might be expected to have some effect on the general **Tissue Change**, through the increased movement of the lymph flushing out the cells and leading to a more complete removal of the waste products. As a matter of fact, some increase in the nitrogen and sulphur eliminated in the urine has been observed under the use of large quantities of water, but it is impossible to estimate at present how far this may be due to the diuresis alone; in any case the increase is not by any means so large as is often believed, as it only amounts to some 5 per cent. or less. Any salt solution causing an acceleration in the movement of the fluids of the body must tend to facilitate the excretion of the waste products in the same way, but some recent investigations indicate that in addition salt tends to alter the protein metabolism through acting directly on the cells; this action is so slight, however, that the resulting change in the nitrogen eliminated is concealed by the increase caused by the more complete flushing and diuresis. The amount of proteins and fats absorbed from the alimentary tract does not appear to be altered by the administration of large amounts of water (Edsall).

Strong salt solutions injected into animals either hypodermically or intravenously sometimes prove fatal, apparently from the withdrawal of fluid from the central nervous system. The symptoms in mammals are increasing lassitude and weakness, with augmented reflex excitability, tremors, and finally convulsions. The circulation is only slightly affected until just before death, when the blood-pressure falls suddenly. The red blood cells are found to be much shrunken, and hæmorrhages are found in different organs; the lungs are œdematous, and the intestinal mucous membrane is swollen and congested.

The **Salts of the Urine** are increased by diuresis from any cause, as has been stated; both sodium and potassium are augmented but especially the sodium which is present in larger proportions in the serum and therefore forms a larger constituent of the glomerular secretion. This increase in the sodium salts is, of course, particularly marked when diuresis is induced by common salt, but when potassium salts increase the urine, the sodium also generally predominates in it and this would eventually lead to the loss of all the sodium in the blood of herbivora, whose food contains large quantities of potassium; but after a certain amount of sodium has been lost, potassium causes no further excretion, so that the tissues apparently protect themselves from the total loss of sodium chloride, which would be fatal to them.

Bunge states that in both man and animals a diet rich in potassium causes an appetite for common salt, while a diet which does not contain an excess of potash does not develop this desire. Thus herbivorous animals and agricultural peoples seek for salt, because vegetable foods contain large quantities of potassium, while the carnivora and the hunting peoples require no salt and often have a distaste for it, owing to their food containing a larger relative proportion of sodium salts. This instinctive appetite he regards as a means by which nature protects the tissues from excessive loss of sodium. Some doubt has recently been thrown on this explanation of the desire for salt by Lapicque, who discovered some African races living on vegetable substances alone, and using the ashes of the plants, which contain more potassium than sodium, as civilized peoples use ordinary salt. He holds, therefore, that salt is merely of value as a flavoring agent.

Therapeutic Uses.—Water and salt are rarely or never prescribed as such, but are used to a very large extent in medicine, and great virtues have been ascribed to them in a number of pathological conditions.

They are used for their local action, and for the supposed alterations in the tissue-change and in the excretions produced by them after their absorption into the blood. In general, patients are sent to watering places and baths, and the success of the treatment is to a considerable extent due to the climatic conditions, the change in the habits of life, the dietetic treatment and the rest from everyday occupations. At the same time the drinking of large quantities of weak salt solutions, and the constant bathing in somewhat irritating fluids, may exercise a therapeutic action in many cases, and may at any rate aid the hygienic conditions. Whether the water contains salt or not, it must be remembered that in bathing the action is a purely local one, for neither the salt nor the water is absorbed. The slightly irritant effect on the skin may, however, improve its circulation and nutrition, and thereby be efficacious in some skin diseases. By continued use the sensitiveness of the skin vessels to heat and cold may also possibly be deadened. The changes in the metabolism induced by bathing in strong salt solution are merely trifling in extent, and there is no reason to suppose that the bathing in itself has any therapeutic value whatever. The efficacy of the treatment in bathing places is due to the dietetic regimen, the change in climate and other factors, which are popularly supposed to be merely accessory features. Special baths are very frequently recommended for some diseases, but it must be remembered that the action is due to the salt-action; the greater the concentration, the greater is the effect on the skin, and it is of no importance which of the neutral salts is in the solution, or whether small traces of iron or other metals are present; alkaline baths act more on the skin than others.

In diseases of the stomach the drinking of large quantities of water or of weak salt solutions may also be beneficial. The action is similar to that on the skin—a mild irritation, owing to the swelling of the more superficial cells of the epithelium and the increased movement of the fluid in them and in the deeper layers. In some cases of insomnia hot water sometimes causes sleep, probably by causing dilatation of the gastric vessels, and thereby withdrawing the blood from the brain.

In many diseases in which the symptoms point to a disorder of the metabolism, water and salt solutions are advised. Thus gout and rheumatism are frequently treated by sending the patients to watering places, on the theory that the tissues are washed out thoroughly and the waste products thus removed. As a matter of fact, the more recent work in this direction shows that large quantities of water and dilute salt solutions have little or no effect on the uric acid excretion, which was formerly believed to be much diminished. This fact does not necessarily involve the inference that the treatment is erroneous, for it is now generally recognized that gout it not really due to the failure of the uric acid excretion. Many cases are unquestionably benefited by the springs, although it may be questioned how much of the improvement is due to the water taken, and how much of it ought to be ascribed to the changed conditions of life.

The bath treatment has been recommended for numerous diseases in which the salt and water could not possibly have any beneficial action, and in which the remedial agent is the climate, and perhaps the faith of the patient in the water. Belief in the healing power of certain natural waters is one of the most ancient of all therapeutic theories, is found among altogether uncivilized peoples, and has been incorporated in many religions. It is not to be wondered at that in some nervous disorders the faith of the patient and auto-suggestion perform some marvelous "cures."

In obesity the drinking of some waters, such as that of Kissingen or Homburg, has been advised. These waters contain from 0.2–1.4 per cent. sodium chloride, and it seems very doubtful if they have any effects in themselves; many hold that the benefits accruing from the treatment are really due to the hygienic measures followed, and that the waters play only an insignificant rôle.

Salt in solid form or in strong solution is used occasionally as an emetic in cases of emergency, as in poisoning, and generally produces vomiting rapidly, owing to the irritant action on the stomach. In nitrate of silver poisoning it arrests the corrosive action by the formation of the insoluble silver chloride.

Salt solution is often used instead of water in enemata and when concentrated possesses an irritant action on the bowel, producing peristalsis. Strong solutions are sometimes thrown into the rectum to destroy round worms.

Isotonic salt solutions (0.6–0.9 per cent.) are often administered when the body has lost much fluid, as they are rapidly absorbed and are devoid of irritant action; thus in hæmorrhage these solutions are injected subcutaneously, intravenously, or per rectum. A rapid improvement in the circulation follows, and this has given rise to the erroneous opinion that such saline infusions stimulate the heart directly as well as by the mechanical effect of the increase in the fluids of the body; this theory has led to infusions being made in weakness of the heart from other causes than hæmorrhage. Some of the symptoms of cholera are believed to be due to the loss of fluid, and these are said to be relieved by the injection of salt solutions, though the mortality does not seem materially altered. The intravenous and subcutaneous injection of salt solution has been recommended in uræmia and similar intoxications, with the idea of washing out the poisons through the kidneys; the same results can often be obtained by drinking large quantities of water. There is still some question as to whether the infusion of salt solution is really remedial in loss of blood and the latest investigator of the matter, Feis, comes to the conclusion that it is of little or no benefit. The hypodermic injection of large quantities of isotonic salt solution is said by Biernacki to have effects which only pass off in some 6–8 days in animals. The blood was at first much diluted, but afterwards became very concentrated and after a few days a considerable number of the red cells were found in a state of disintegration, and the hæmoglobin thus liberated was distributed through the plasma until it was finally excreted in the urine. The animals did not seem to suffer from the treatment, but his results indicate that the injection of large quantities of salt solutions is by no means the harmless proceeding which it is generally believed to be.

Isotonic salt solutions are used in surgery to wash out the peritoneal cavity, which would be injured by distilled water.

According to a recent view, the retention of sodium chloride in the tissues may lead to the retention of fluid and may thus tend to cause œdema and dropsy. These conditions have therefore been treated by a diet containing a low proportion of salt, and in a certain number of cases with some success. It is still doubtful, however, whether the theory is correct, and the improvement may have arisen from other factors than the restriction of chlorides in the food.

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II. POTASSIUM SALTS.

The effects of potassium in the organism can best be studied by administering the chloride, as the Cl ion is practically devoid of action and the symptoms induced by potassic chloride must therefore be due either to the "salt-action" or to the potassium. The salt-action can be discounted by comparing the symptoms with those of an isotonic solution of sodium chloride, and when this is done it is found that potassium has a distinctly poisonous action, which is chiefly manifested in depression of the central nervous system and of the heart.

In the frog the central action is shown by the spontaneous movements becoming weak and slowly performed, and by their completely disappearing much earlier than in sodium chloride experiments. In mammals the chief nervous symptoms are great muscular weakness and apathy. The respiration becomes rapid and labored, probably from the anæmia of the centres, and death is often preceded by weak asphyxial convulsions.

The depression of the heart is shown in the frog by weakness, slowness and irregularity when chloride of potassium is injected subcutaneously, but is more clearly demonstrated by the rapid failure of an excised heart when a chloride of potassium solution is perfused through it. An isotonic solution of common salt also brings the heart to standstill after a time, but potassic chloride acts very much more quickly, and, in fact, the former may restore the heart beat after it has been stopped by potassium, which proves conclusively that the latter has a specific poisonous action in addition to any salt-action. Ringer, however, found that the beat of the frog's heart perfused with a solution of common salt was not so satisfactory as that of one perfused with the same solution to which some potassic salt had been added, because, as has been already mentioned, the proteins of the heart must contain potassium, and when this is substituted by sodium, as is the case when there is no potassium in the perfusion fluid, the muscle becomes incapable of normal contraction. (See Calcium.)

The mammalian heart is also injured by the action of potassium when the salt is administered in large quantities, as is shown by the pulse becoming much slower and weaker and by a sudden fall of blood-pressure; an acceleration of the pulse is often observed at first. The poisonous action of potash on the heart has given rise to exag-

Salt action irritation of nerves + muscles at first then strong depression
Irritation specific in part. A strong diuretic.

gerated apprehensions of the danger of using its salts in therapeutics, and it may therefore be noted that potassium has no effect on the heart when given by the stomach, and that very much larger quantities of potash are taken daily in the food by thousands of persons than are ever prescribed in medicine. Bunge estimates the amount of potash in the food of some classes at 50–100 grms. (1½–3 oz.) per day. Meltzer has recently shown that the magnesium salts are much more poisonous than those of potassium, yet magnesium sulphate is often employed in doses of ½–1 oz. without deleterious effects. The absence of effects from the potassium ion when the salts are taken by the mouth is due to their rapid excretion in the urine.

The failure of the heart is the cause of death in mammals when potassium salts are injected into a vein, the respiration and the reflexes often persisting for a few seconds afterward. According to Braun, potassium salts cause a transient contraction of the vessel walls when they are injected directly into the arteries.

Potassium has some action on muscle in the frog, the contraction seeming to be somewhat greater in height, though shorter in length, and there being less tendency to contracture. Muscle exposed in a solution of potassic chloride dies very much sooner than in an isotonic solution of sodium chloride.

Chloride of potassium has also some depressant action on the peripheral nerves, for they lose their irritability rapidly when they are exposed to its solutions. A concentrated solution applied to an exposed nerve causes contractions of the muscles which are supplied by it, but these are weaker and last a much shorter time than those elicited by a similar solution of common salt. This is explained by the depressant action of the potassium opposing the irritation which it induces through its salt-action.

The absorption of potassium salts is followed by the same changes in the movement of the fluids of the body as have been described in the case of sodium chloride (page 490). This generally results in diuresis with an increase in the potassium and the sodium and chloride in the urine. The potassium salts are generally credited with greater diuretic properties than those of sodium, and there is reason to believe that they lie midway between the sodium salts and the sulphates in their behavior to the renal cells (page 491). Strong solutions of potassic chloride are said to be more irritating to the stomach and also in the subcutaneous tissues, than those of sodium chloride; this would indicate that potassium has a specific irritant action apart from its salt-action, which is not unlikely, although it cannot be said to have been demonstrated satisfactorily as yet.

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Lithium, Cæsium, Rubidium.

In regard to the action of the rarer alkalies, Lithium, Cæsium and Rubidium,[1] comparatively little is known. They seem to have some effect in depressing the spinal cord in the frog, but it is uncertain whether this is, like the action of sodium chloride, merely due to the presence of large quantities of salts in the body, or whether they have a specific action on the nerve cells. Lithium seems to have some further depressant action on the motor nerves, and to weaken the muscular contraction. It acts much less powerfully on the mammalian heart than potassium, but has some effect in weakening it. Its chief effects are exercised in the alimentary tract, for gastro-enteritis and extravasations of blood into the stomach and bowel are induced by its subcutaneous or intravenous injection and these are the cause of death in fatal poisoning in animals. Such violent effects are less easily elicited by the administration of lithium by the mouth, though vomiting and purging have been caused in animals by this method also, and disturbance of the alimentary tract has sometimes followed lithium treatment in man. Some of the lithium is excreted in the bowel, and in this respect this metal appears to form a contrast to potassium and sodium and to resemble rather the group of alkaline earths. Most of it appears in the urine, however, and here the excretion is slow, for traces may be found in it for many days or even weeks after a single administration.

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[1] The still rarer metals Yttrium, Erbium, Beryllium, Didymium and Lanthanum have scarcely received examination except at the hands of Brunton and Cash, and are not of sufficient importance to require further mention here.

Rubidium seems to act on the frog's heart and on muscle cells in much the same way as potassium. It is slowly excreted by the kidney; traces are found also in the fæces, especially if diarrhœa occurs, as is not infrequently the case.

Cæsium resembles lithium in causing inflammatory reactions in the alimentary tract, leading to vomiting and diarrhœa, when it is injected hypodermically or when large doses are given by the mouth. It is partly excreted along the alimentary tract in mammals. In the frog it induces weakness of the muscles and paralysis.

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III. AMMONIUM.

Although ammonium is not a metal, its behavior in the body resembles in many points that of the fixed alkalies, and it may therefore best be studied along with them. The ordinary solutions of ammonia and the gas itself are possessed of powerful irritant properties, and its general action can be determined only by the examination of those of its salts in which, as in ammonium chloride, the effects of the anion can be neglected. The action of chloride of ammonium is due to the specific action of the base and to the salt-action.

Action.—Its most striking effect is the stimulation of the **Central Nervous System**, which is induced when it is injected subcutaneously or intravenously. The reflex irritability is much increased, and this may be followed by tetanic convulsions, both in frogs and mammals. These convulsions persist after division of the cervical spinal cord and destruction of the medulla oblongata and brain, and are evidently caused by changes in the spinal cord, similar to those met with in strychnine poisoning. The medullary centres are also involved, for the respiration very often ceases for a moment, and then becomes very much accelerated, and in some instances deeper. The cause of the altered breathing is a stimulation of the respiratory centre; the preliminary pause is attributed by some to action on the vagus ends in the lungs, but this is denied by others, and it seems possible that it is due to excessive stimulation of the respiratory centre.

The blood-pressure rises from contraction of the peripheral arterioles, induced by stimulation of the vasomotor centre, while the heart is sometimes slowed from increased activity of the inhibitory centre, but is said to be accelerated in other cases; whether this arises from action on the cardiac muscle or on the accelerator centre is still unknown.

During the convulsions the respiration is arrested and the blood-pressure becomes extremely high. If large enough quantities be injected, the stimulation is followed by paralysis of the central nervous system and the animal dies of asphyxia, but if artificial respiration be carried on, it recovers rapidly, from the salt being eliminated.

In the frog ammonium chloride tends to paralyze the terminations of the **Motor Nerves**, but little or no such action is met with in mammals. This marked curara-like action differentiates the ammonium tetanus of the frog from that seen under strychnine, as the spasms last a shorter time, and soon become weaker from the impulses failing to reach the muscles through the depressed terminations. The **Muscles** themselves are also acted on by ammonium in much the same way as by potassium, although in the case of ammonium a preliminary stage of somewhat augmented irritability has been observed by some investigators. Ammonium chloride is generally credited with acting on the **Secretions** of the stomach and of the bronchial mucous membrane, which it is said to render more fluid and less tenacious, and at the same time to increase considerably.

Ammonium salts penetrate most cells of the body more freely than the salts of the fixed alkalies, and solutions of ammonium chloride are therefore **absorbed** more rapidly from the stomach and intestine than those of sodium or potassium chloride. They permeate into the blood cells with still greater freedom, and, in fact, solutions of the chloride of ammonium meet with little more resistance in entering the red blood corpuscles than does distilled water. If ammonium be combined with a non-permeating ion it penetrates the blood cells or the intestinal epithelium with difficulty, however, so that the sulphate of ammonium is slightly cathartic, although less so than the sulphates of the fixed alkalies. (See Saline Cathartics.) The epithelium of the lungs appears to be impermeable by the ammonium ion, so that when ammonia is inhaled it does not reach the blood, and when it is absorbed from the alimentary tract it does not appear in the breath (Magnus).

When ammonium salts are taken by the mouth, they have little or no tendency to cause symptoms from either the central nervous system or the heart. No case is known in which convulsive attacks could be shown to be due to the direct action on the central nervous system in man, and it is very doubtful whether the circulation is affected at all. In some cases of poisoning with ammonium hydrate convulsions have occurred, but these seem to be due to the violent local action of the anion. The chloride of ammonium may induce irritation and vomiting when taken in large quantities into the stomach, but only through its salt action.

Excretion.—Some of the ammonium salts are excreted unchanged in the urine, while others are changed to urea. This transformation, which probably takes place in the liver chiefly, proceeds very rapidly, so that considerable quantities of some salts may be injected slowly into a vein without inducing any symptoms whatever. In the herbivora, urea is formed whatever salt of ammonia is injected, but in the carnivora and in man this is true only of the carbonate and the salts which are oxidized to the carbonate in the body, such as the acetate and citrate. The explanation seems to be that in the herbivora the abundant fixed alkali of the blood and tissues displaces the ammonium of such salts as the chloride, and the carbonate of ammonium thus formed is changed to urea. In the carnivora and man, the supply of fixed alkali being less abundant, the ammonium chloride is not changed to the same extent, but is excreted as such in the urine. In the herbivora the administration of ammonium chloride is therefore followed by an increased elimination in the urine of urea and of the chlorides of sodium and potassium which are formed by the interchange; at the same time the fixed alkalies of the blood are reduced in amount, and this may give rise to serious symptoms (see Acids). In the carnivora and man chloride of ammonium does not increase the urea appreciably, but is excreted as such in the urine.

The urine is often increased by the exhibition of ammonium salts, but not always. It is to be noted that, while the alkaline salts of the fixed alkalies render the urine less acid or even alkaline, ammonium salts have no such effect, because they are excreted as urea or as neutral salts.

In birds and reptiles ammonia is apparently excreted as uric acid.

The **Substituted Ammonias** of the methane series, such as methylamine, and some of those of the aromatic series resemble ammonia in their general effects, but the stimulation of the central nervous system is not often so marked. In general terms, those compounds in which one hydrogen atom is substituted, tend to cause greater nervous stimulation than those in which two or three such substitutions are made, while this action is again more prominent in those in which four alkyl groups are combined with the nitrogen. In addition, most of these compounds seem to have a more depressant action on the central nervous system afterwards than ammonia, and they all tend to weaken and eventually paralyze the terminations of the motor nerves.

The ammonium bases formed from the natural alkaloids appear to have less action on the central nervous system, but act like curara on the terminations of the motor nerves.

PREPARATIONS.

Ammonii Chloridum (U. S. P., B. P.) (NH_4Cl), 0.3–1 G. (5–15 grs.), in solution.

Trochisci Ammonii Chloridi (U. S. P.), each containing 0.1 G. (2 grs.) of ammonium chloride with 0.2 G. (4 grs.) of liquorice extract and some syrup of Tolu.

Therapeutic Uses.—The chloride is prescribed chiefly for its effects on the respiratory mucous membranes, and is a very common constituent of expectorant mixtures for bronchitis and catarrh. The lozenge is often used for sore throat, and chloride of ammonium solutions are occasionally inhaled or sprayed into the throat. It has also been prescribed in gastric catarrh with benefit in some cases, but whether this is due to its acting on the mucous secretion is unknown.

Ammonium chloride and the chloride of trimethylammonium were at one time advised in rheumatism, but have proved useless in this disease.

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IV. BROMIDES.

It was formerly widely believed that the bromides had no further action than the chlorides, and that any effects observed from potassium bromide were due to the potassium ion, the bromide ion being indifferent. There is now no question, however, that the bromides have distinctive effects, for the bromides of potassium, sodium, lithium and other metals induce changes in the central nervous system, which are not elicited by the chlorides.

Symptoms.—The bromide of potassium is the salt most generally used, and its action has been more carefully described than that of the other bromides.

KBr — bitter salty taste — salivation, thirst; / much, vomit. vomit.
Headache, lassitude, weakness, physical + mental apathy, tending to sleep (not deep)
+ drowsiness + fatigue following. Reflexes reduced. Chronic = bromism — skin
eruptions, esp acne of face, may fuse to ulcers, erythema. local disturbance of digestion
Rarely resp passages. (give delayed + [illegible] [illegible] [illegible])
Loss of memory, apathy + inaccuracy of speech. Hesitancy. Gait uncertain.

In the **Alimentary Tract** it acts in the same way as the chloride of sodium, possessing a bitter salt taste and inducing salivation and thirst, and in large quantities irritation of the stomach, nausea and vomiting. Occasionally diarrhœa has been observed from concentrated solutions reaching the intestine.

General Symptoms.—Apart from these results of local irritation, the first symptom is often a dull, heavy headache, with a feeling of lassitude, fatigue, disinclination for exertion, mental or physical, and often muscular weakness. Thought is slow and confused, the memory is indistinct, ideas are put into words with difficulty and the speech is accordingly slow and hesitating. External objects and movements are perceived, but arouse no interest in the patient, and very often this state of apathy passes into drowsiness and sleep. The bromides, however, have not the sleep-compelling power of morphine or chloral, and the sleep is never very deep and is not refreshing, the patient sometimes feeling dull and unfit for exertion after it, and some mental confusion often persisting for several hours after awaking. The reflexes are much depressed by large doses of bromide, so that touching the back of the throat does not induce nausea, although the sensation of touch may persist. The mucous membranes of the genito-urinary tract are also less sensitive, or rather their irritation is less liable to set up reflex movements. After very large doses of the bromides the conjunctiva may sometimes be touched without causing winking, and lessened sensation in the skin has been noted in some cases.

The pulse and respiration are slower than usual after large doses, but scarcely more so than in sleep. An increase in the urine is often observed.

Acute fatal poisoning with bromides has seldom or never occurred in man, but after enormous doses prolonged sleep or stupor has been seen, and confusion and apathy lasting for several days.

When bromide is given repeatedly in large doses, a series of symptoms is often induced to which the name of **Bromism** has been applied. It occurs much more rapidly in some persons than in others, and may suddenly appear after the patient has been taking the drug for months without any untoward results. The commonest symptoms of bromism are *skin eruptions* of various kinds, very often commencing as acne of the face. In severe cases the pustules of acne may coalesce and form small abscesses, which are followed by ulcers. In other cases the skin affection partakes rather of the nature of a localized blush or erythema and sometimes copper-colored blotches have been observed. Some *disturbance of the digestion* and loss of appetite is often met with from the local action of large quantities of the salt on the stomach. Affections of the *respiratory passages* are not produced so often by the bromides as by the iodides, but have been met with, and consist in an increased secretion of mucus by the bronchial and nasal epithelium. The *mental symptoms* are merely exaggerations of those observed after one large dose. The memory is especially defective, Some of these may be due to K. Mental sym = direct action. Irrit of motor areas of brain reduced, no poison convulsions localized

sometimes sudden lapses occurring, sometimes a general inability to remember the most recent events being met with. The patient is indifferent to his surroundings, speaks slowly and stammers, mispronounces ordinary words or misses several words out of a sentence. The gait is uncertain and tremor often accompanies any movement, the expression of the face is stupid and apathetic, and the eyes are heavy and lack lustre.

These symptoms generally disappear on the withdrawal of the drug, but in his reduced condition the patient is of course liable to fall a victim to infectious disease, and in a number of cases of chronic bromide poisoning the immediate cause of death has been an attack of bronchitis or pneumonia.

Action.—The effects of the bromides on animals have been the subject of a large number of researches, but these have not been attended with success in most cases, because the investigators have almost always used the bromide of potassium. The action here is complicated by the potassium action as well as by the salt-action, and these are often sufficient to obscure the slight depression of the brain which is the really characteristic effect of the bromide ion. In the frog, for example, potassium chloride is capable of inducing depression of the central nervous system, and a certain amount of stupor is induced by the salt action of chloride of sodium. The slightly greater depression induced by the bromide may well be overlooked, therefore, and many investigators have concluded that the bromide ion is as inactive as the chloride. The typical bromide action may be induced with greater clearness in mammals by the use of sodium bromide in repeated doses, and in dogs symptoms of depression and imperfect coördination have been observed, and sometimes stupor and death from failure of the respiration. The most characteristic action, however, is obtained from the administration of the drug to patients, as the affection of the central nervous system is so slight after all but extreme doses that in order to produce distinct symptoms in the less sensitive brain of the dog, quantities must be used which entail the additional complication induced by salt-action.

The irritation of the throat and stomach, the nausea, vomiting and rarer diarrhœa must be attributed for the most part to the action of the salt in withdrawing fluid from the mucous membranes, and may be avoided by the use of dilute solutions and by their administration when the stomach is full.

The depression and other mental symptoms are due to a direct action on the **Central Nervous System.** Albertoni found that the irritability of the motor areas of the dog's brain was very distinctly reduced by the administration of bromides, and in particular that a stimulus which normally would have spread over a wide area and given rise to an epileptiform convulsion, caused only localized contractions after bromides, while convulsive poisons entirely failed to act. Loewald found some psychical processes, such as those involved in the addition of numbers, uninfluenced by bromides, while a series

Reflexes absent - while back of throat - no nausea. Only on large doses
is sensation diminished. | Resp. slow, sex desire gone. This is due to Br ion.
Heart directly affected by large doses - ~~If~~ often Kation. Skin eruptions from glands

of figures could be learned by rote only with great difficulty; he therefore considers that the action is limited to certain definite functions. The reflexes are also reduced very considerably by bromides, and according to many observers the passage of impulses from the sensory to the motor cells of the cord is interrupted, while the connection between the cerebral centres and the motor cells of the cord is maintained intact. In man the most striking instance is the absence of reflex nausea when the back of the throat is touched. The other reflexes are also reduced, especially those of the genital organs, those of the conjunctiva being less affected. While reflex movements cannot be elicited, the sensation often remains unimpaired, but after large doses a more or less complete anæsthesia is said to be produced. This anæsthesia extends to the skin when very large quantities are administered, and the cutaneous nerves are said to be rendered somewhat less acutely sensitive, when comparatively small doses are taken.

The depression of the spinal reflexes effected by the bromides renders them antidotal to strychnine, which induces convulsions only when given in much larger quantities than are usually necessary.

In addition to the ordinary reflexes, some special functions are depressed by the bromides. Thus the respiration becomes slower, and the sexual instincts are depressed or entirely suspended in many cases. Whether the latter is caused by action on the spinal cord or on the cerebral cortex is unknown.

The action on the central nervous system is due to the bromide only, and not to the base with which it is combined. Thus, it may be elicited by the bromides of potassium, sodium, lithium or ammonium, while it is not induced by their chlorides.

The bromide ion is not very poisonous to **Nerve** and **Muscle**, but it is not so nearly indifferent to them as the chloride ion, although no effects are elicited unless the bromide is applied directly to the exposed muscle or nerves.

The **Heart** is not affected directly when bromides are given even in large doses by the mouth; when the potassium salt is injected intravenously in animals, the characteristic effects of the potassium ion are seen in the heart, but these are not elicited in therapeutics. The vessels of the pia mater are often found contracted from the action of bromides, but this anæmia of the brain is analogous to that observed in sleep and it may therefore be the result and not the cause of the depression. The mental disturbance observed in bromism is so nearly related to that seen after a single large dose that it is unnecessary to enter into any explanation of it here.

The **Skin Eruptions** arise in the great majority of cases from the glands, and in fact generally remain confined to them. Bromide has been found in the acne pustules, but the old view that the acne is due to bromine being freed in the glands is undoubtedly incorrect.

The **Temperature** of animals is often said to be reduced by the bromide; this may be explained by the lessened movement.

Excretion.—The bromides are rapidly absorbed by the mucous mem-

Very slow excreted in urine – accumulates to a limit, replacing NaCl chiefly in blood (also in brain + cord), so sympt. reduced by feeding chlorides also excreted in milk(!) + perspiration.

branes, and some bromide reaction can be obtained from the urine a few minutes after they have reached the stomach, but the great mass of the drug is very slowly excreted. Thus, after a single dose of 30 grs. the urine was found to contain bromide for two months, only about 10 per cent. being eliminated in the first 24 hours. When the treatment is continued, the bromide therefore tends to accumulate in the body, but the proportion excreted rises with the increase of the salt in the blood, until an equilibrium is reached, exactly as much bromide appearing in the urine as is absorbed from the stomach. The excretion continues after the treatment is discontinued, and the drug is found in the urine for one or two months afterwards. When the body is thus saturated with bromides, some of the chloride combinations are replaced by them; for example, Nencki found that the acid secreted by the stomach might contain more hydrobromic than hydrochloric acid. The chlorides are excreted in much larger quantity than usual in the urine. The nitrogenous metabolism does not seem to be affected, but in some cases a considerably smaller amount of phosphates appears in the urine. This has been supposed to be related to the action of bromides in lessening the mental activity, but is not by any means a constant effect.

The bromides seem to be distributed in the body very much in the same proportions as the chlorides, being most largely found in the blood serum, while the brain and spinal cord contain them in comparatively small proportion. The whole behavior of bromide in the body indicates that most of the tissues are unable to discriminate it from the chloride. Thus its administration is followed by an excretion of halogens partly chloride and partly bromide. And if it were possible to follow the course of the individual chloride ions in the body after the administration of common salt, their stay in the body might probably be as long as that of the bromide, the chloride first excreted being furnished by the salts of the blood and tissues. The reduction of the chlorides may be the cause of some of the symptoms in bromism, and Wyss states that the symptoms in rabbits may be immediately relieved by the intravenous injection of chlorides. It has not been shown as yet that the cerebral effects of the bromides in man are due to this, however, and the bromide ion may have a specific depressant action here.

The bromides are excreted mainly in the urine, but traces occur in the perspiration and milk, and some cases of bromism in children have been recorded as due to their absorbing the bromide thus excreted by the nurse. In chronic poisoning the breath very often has a disagreeable odor, which has been attributed to bromine or some of its volatile organic compounds being excreted by the lungs, but nothing is known with certainty regarding it. Bromine has also been found in the hair after the prolonged use of bromides, and is supposed to exist in organic combinations here. The hydrobromic acid secreted into the stomach in bromism is probably all reabsorbed in the intestine.

KBr 1-4 G. All sol – give well diluted, flavored with vol. oil + syrup. [illegible] for hypo.
Specific for epilepsy – lessened no. of attacks – only while drug administered.

Bromide of Sodium differs from bromide of potassium chiefly in the absence of any changes in the heart or in the muscles exposed to its solution. But these occur only in animal experiments and the action in man is identical.

Bromide of Ammonium owes most of its action to the bromide ion, unless when it is given in large quantities, when, according to several observers, the convulsive action characteristic of ammonium is developed in animals. Smaller doses are followed by lethargy and weakness in animals, and in man the effects are practically identical with those of sodium bromide.

Lithium Bromide has not been so largely used as the others, and is liable to cause digestive disturbances from the lithium action (see page 497).

Hydrobromic Acid possesses the characteristic bromide action after absorption, but has the local action of an acid and is consequently more irritant than the other members of the series.

Strontium and **Calcium Bromides** resemble the others in their general action and are quite superfluous.

PREPARATIONS.

1-4 G

POTASSII BROMIDUM (U. S. P., B. P.) (KBr), 1–4 G. (15–60 grs.).
~~SODII BROMIDUM~~ (U. S. P., B. P.) ($NaBr$), 1–4 G. (15–60 grs.).
Ammonii Bromidum (U. S. P., B. P.) (NH_4Br), 1–2 G. (15–30 grs.).

Acidum Hydrobromicum Dilutum (U. S. P., B. P.) contains comparatively little bromide, as it is only a 10 per cent. solution in water, so that a gramme of potassium bromide contains as much bromine as about 7 grammes of the dilute acid. 4 c.c. (1 fl. dr.).

The bromides are all colorless crystalline bodies without odor but with a saline, bitter taste, and are very soluble in water. They are almost always prescribed in solution and ought to be taken diluted with a considerable amount of water in order to avoid the irritant action on the stomach. The prescription may be flavored with syrup and with some of the volatile oil preparations. The large doses of the bromides render their hypodermic injection inadmissible, as concentrated solutions provoke pain and irritation in the subcutaneous tissues.

A number of other bromide combinations are used in therapeutics, such as the hydrobromide of quinine, but here the bromide ion is present in very small quantity compared with the alkaloid, and in the doses used in therapeutics has no appreciable effect. In monobromated camphor the bromine is present in a different form and no bromide ion is liberated, so that the action of the metallic bromides cannot be compared with it. As a matter of fact, the bromine in this compound seems to have little or no effect. *Sabromine,* the dibrombehenate of calcium ($((C_{22}H_{41}O_2Br_2)_2Ca)$), has been introduced as a substitute for the alkali salts.

Therapeutic Uses.—The bromides are used chiefly in the treatment of epilepsy, in which they cannot be replaced by any other drug, and the prognosis of which has been entirely changed since their introduction. In a few cases the bromide treatment is said to cure epilepsy—the attacks do not return after the treatment is stopped—but this is exceedingly rare; in others the bromides have no effect, but in the great majority of cases (90–95 per cent.) the number of attacks is

May have to wait for effect till tissues saturated (3 days). Start with small doses, up to 10 G. or when skin eruption is. NaCl facilitates Br excretion. Treat acne with As + cleanliness. [illegible] Use as soporifics - thus less chloral needed. In neuralgia, in worry, nausea seasickness, lessens reflex movements

much smaller, or the patient may be entirely free from them as long as the treatment is persevered with, although they return as soon as it is given up. Very often no improvement is observed during the first few days, until the tissues have become saturated with bromide, but in other cases the spasms disappear immediately. The bromide of potassium is more commonly used than the others, and the general impression is that it is more efficient and more certain in its effects, but some physicians prefer the bromide of ammonium or of sodium, and others still prefer a mixture of two bromides. In severe cases it is sometimes found that the bromide action is strengthened by the addition of cannabis indica, opium or chloral, although the last two are to be used with caution. In the treatment of epilepsy it is well to begin with small doses and to increase them up to 10 G. per day, or until the desired effect is attained, or some complication, such as widespread skin affections, precludes their further use. When little chloride is taken in the food the excretion of bromide is much retarded, and, on the other hand, the addition of chloride to the dietary accelerates the bromide excretion. The restriction of the salt in the food of epileptics under bromide treatment has therefore been suggested with the object of saturating the tissues with smaller doses of bromide than would otherwise be necessary. In practice, however, it is difficult to reduce materially the chlorides of the food, and equally satisfactory results may be obtained, with less hardship to the patient, by slightly increasing the dose of bromide.

The acne is very often a troublesome accompaniment of the bromide action, and in fact may prevent the use of this valuable drug in otherwise suitable cases. It may often be prevented by scrupulous cleanliness of the skin and frequently yields to treatment with small doses of arsenic.

The bromides are not so effective in other affections of the central nervous system, although some success has attended their use in chorea, in the convulsions of children, and in some forms of hysteria. They have also been used in tetanus and in strychnine poisoning, but are inferior to other remedies, such as chloral. Neuralgia is sometimes improved by bromide treatment, especially when it arises from worry, anxiety or overwork.

As soporifics, bromides often fail entirely or induce such depression and confusion subsequently as to preclude their use. In sleeplessness from anxiety they are often valuable, however, and it is found that the dose of chloral may be considerably lessened if it is prescribed along with bromides. In sleeplessness from pain bromide is of little or no value.

Bromides have been used with good results in sea-sickness, in the sickness of pregnancy, and, it is said, in whooping-cough. Bromide of potassium was formerly given internally to lessen the reflex movements of the throat and thus to permit of laryngoscopic manipulations, and it was also applied locally to the throat for this purpose. It has now been superseded by the local use of cocaine.

Iodides. Obscurity; idiosyncrasy. Gastric irritation, vomiting due to salt action. Iodism if long used — catarrh of resp passages — watery secretion & sneezing. Mucus of bronchi increased. May affect tonsils. conjunctiva, frontal sinus. Swollen throat, salivation. Increase of gastric juice

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V. IODIDES.

Although the iodides have been more largely used in medicine than any of the other salts of the alkalies, their mode of action is still wrapped in obscurity. This is due to the unsatisfactory state of the pathology of the diseases in which they are used, to the fact that the attention of investigators has been drawn to the symptoms of poisoning rather than to the therapeutic action, and also to the fact that the effects seem to vary very considerably not only in different individuals, but also in the same person at different times.

Symptoms.—Large quantities of the iodides cause irritation of the stomach from their salt-action and induce nausea and vomiting, more rarely diarrhœa; but these symptoms are quite distinct from those known as **Iodism,** which may arise from comparatively small quantities, and which are most commonly seen when the remedy has been administered repeatedly.

The commonest symptom of iodism is catarrh of the **Respiratory Passages,** more especially of the nose, which betrays itself in some swelling and discomfort in the nasal mucous membrane, in a profuse watery secretion and in sneezing. The catarrh spreads upwards to the conjunctiva, which often becomes swollen and congested, and to the frontal sinuses, where it induces a feeling of dulness or violent headache; it also progresses downwards to the tonsils, which become swollen and inflamed in some cases. Still lower it occasionally causes some swelling and œdema or small ulcers in the larynx, and has thus caused dyspnœa, which has necessitated tracheotomy, or very rarely has proved fatal. Bronchitis has also been observed in man, with a profuse watery secretion, and in animals œdema of the lungs and pleuritic effusion have been produced by the injection of iodides. Even small quantities injected intravenously increase the mucus secreted by the bronchi.

In the **Mouth** iodism is often betrayed by swelling and irritation of the throat and tonsils and by salivation, rarely by swelling of the salivary glands. The stomach is seldom affected, the appetite generally remaining good, but in some persons iodides induce nausea and gastric discomfort. A single dose of iodide increases the amount of gastric juice and prolongs the secretion aroused by the taste of food.

Skin Eruptions of different forms are also common results of the

All sorts of skin eruptions. Diuresis by salt action. If thyroid overactive thyroidism — excess iodides. Symptoms (see below). Much individual variation. Renal inflammation may retard ~~[illegible]~~ elimination. Chil. less susceptible. Tolerance

administration of iodides, but are less liable to occur in the beginning of the treatment than the catarrh of the respiratory passages. These eruptions may simulate almost all known skin diseases, but the most common forms are erythematous patches, or papular eruptions which may pass into pustules or into larger inflamed areas. Eczema, bullæ, pemphigus and purpura arise less frequently from the use of iodides. In some cases a more or less defined area of œdema has been observed in the face.

The **Secretion of Urine** is generally increased by the administration of iodides, ~~as of other~~ salts of the alkalies, though they seem to have no specific action on the kidneys. In rare cases albuminuria has been observed, and some irritation of the bladder, urethra and vagina is said to have been induced by iodide treatment, but these statements require confirmation.

In abnormal conditions of the thyroid gland the iodides and many other iodine compounds often give rise to a series of symptoms which are due to the excessive production of the specific secretion of the gland, which itself contains iodine; these symptoms are quite distinct from those described as iodism and may rather be referred to as thyroidism. Among these symptoms are acceleration and palpitation of the heart, tremors, nervousness, sleeplessness and disorders of sensation, such as localized anæsthesia or neuralgic pains. Sometimes some fever or accelerated metabolism leading to loss of weight has occurred, and occasionally extreme emaciation and cachexia with mental depression, which only abated slowly on the abandonment of the treatment, or which in rare cases were permanent.

In many instances small doses of iodide may be given repeatedly without any noticeable disturbance, but in others the smallest quantity (0.2 G.) induces severe poisoning. Some authorities consider that these small doses are more liable to cause iodism than larger ones, but this may be doubted, as the action of the drug is so capricious that the statistics of different observers show great discrepancies, even when approximately the same dose has been given. Thus, Haslund, treating patients with at first 3 G. (45 grs.) and then 5 G. (80 grs.) daily, observed iodism in only 12 per cent. of his cases during the first few days, while others have found iodism induced in 60 per cent. of their cases after a single dose of 3 G. An attempt has been made to explain these discrepancies by supposing that iodism is only produced by impure iodides, but this is not correct, for it has been observed in numerous cases in which the drug was absolutely pure. Among other conditions which favor the onset of symptoms is a slow excretion of the iodide such as is observed in some forms of renal irritation. Children seem less liable to suffer from the iodides than adults. The dose administered has, of course, some relation to the onset of symptoms; thus, very large doses are more likely to induce them than very small ones, but it seems that a tolerance is soon established in some cases, for after iodism has been induced, and the daily dose lessened accordingly, it is sometimes found that it may be gradually increased ypervariable action. I ion, not the basic ion, is active. Absorption in water from m. m. (not from skin. Excreted by urine in a few minutes! 65-80% in urine in 24 hours. Some in secretions etc. After treatment of medication, most salts in blood & in thyroid. Not in other organs.

Diseased organs take up more. I set free in blood, combines with proteins, esp in thyroid

until a quantity considerably greater than that originally given may be taken with impunity. In other instances, a definite quantity may be given for a long time without inducing symptoms, but these may suddenly set in without any apparent change in the treatment and without any appreciable cause. Very often it is found that the symptoms disappear when the treatment is continued, and recovery invariably sets in when the drug is abandoned. The iodides all induce iodism, the symptoms being apparently unaffected by the basic ion. The condition is seldom dangerous, but a few cases are recorded in which œdema of the larynx resulted and proved fatal, and in others death was attributed to the iodides, but the exact cause was not ascertained.

The iodides are not **Absorbed** from watery solutions applied to the skin, but are rapidly taken up by all the mucous membranes. When given by the ~~mouth they~~ are absorbed unchanged by the stomach and ~~intestine, and appear~~ in the secretions within a few minutes. The greater part of the iodide is **Excreted** in the urine, in which it appears as salts. Some escapes by the salivary glands, however, and small quantities are excreted by the stomach as hydriodic acid and sometimes as free iodine; iodide has also been found in the tears, perspiration, milk, sebum and in the secretion of the nasal mucous membranes. No iodine can be detected in the breath of animals poisoned with iodides. After treatment with potassium iodide, iodine has been detected in the hair, milk, muscles and heart in organic combination. Iodides are much more rapidly excreted than bromides, for 65–80 per cent. of the iodide appears in the urine within 24 hours after its administration, and no iodide reaction is obtained from any of the secretions a week after the treatment has ceased. It has been stated that iodide fails to pass into the serous cavities in inflammatory transudates, but this seems to be incorrect, although the starch test often fails here from the presence of proteins. After iodide medication most of the salt is found in the blood, while comparatively little appears to be taken up by the organs except by the thyroid gland. Small quantities are found in the lungs, kidneys and lymph glands, none in the brain or fatty tissues; diseased organs are said to take up more than sound ones.

The greater part of the iodide administered therefore passes through the tissues and is excreted ~~in the urine in the form of~~ salts. Some of the iodide undergoes decomposition in the body, however, for free iodine has been shown to be excreted into the stomach, and an organic compound of iodine exists in the hair and in various internal organs after iodide treatment. The successful treatment of goitre with iodide of potassium is also a strong argument in favor of the presence of free iodine, and the iodine of the thyroid glands has been shown to be increased by potassic iodide. When iodine is thus liberated in the body, it does not circulate as such, but at once combines with the proteins, and its presence can no longer be demonstrated by the ordinary tests.

Iodides don't effect nervous or circ. systems any more than any other K salts. Metabolism as a rule little affected

The formation of free iodine from iodides (which is, of course, quite distinct from their dissociation into potassium and iodide ions) has been explained by several theories. The first of these assumed that the iodide was decomposed by the carbonic acid of the blood, forming hydriodic acid, and that this was subsequently oxidized in the blood to free iodine. Binz supposed that the decomposition occurred rather in the protoplasm of the tissues, and supported his statement by an experiment in which an iodide solution was saturated with carbonic acid and had plant protoplasm added to it, after which it gave the ordinary iodine reaction with starch. The objection has been raised that this experiment succeeds only when dying protoplasm is used, and another theory has been proposed, namely, that the oxidation is carried on, not by the protoplasm itself, but by some unstable substances which are excreted by living matter, and which therefore occur on the mucous membranes, in the saliva and elsewhere. These bodies are in themselves reducing agents, but in the presence of air, as in the respiratory passages, their oxidation is accompanied by the liberation of "active oxygen" which in turn oxidizes the iodides. Another explanation which has been given for the occurrence of free iodine is the action of nitrites, which decompose iodide of potassium in the presence of acids. But Anten found that iodism is not induced more readily in a susceptible subject when the nitrites are augmented in the tissues. It has been stated recently that iodism is very readily elicited in patients whose saliva contains much sulphocyanide, and that the occurrence of this body in the secretions of the respiratory tract is responsible for the manifestations of irritation induced by iodides. Binz has found that some microbes are capable of setting iodine free from acid solutions of the iodides.

Iodine is supposed to be set free along the mucous membrane of the respiratory passages and in the skin; and in this way the coryza of the former, and the eruptions on the latter are explained. It must be noted that free iodine has not yet been clearly demonstrated on either of these surfaces, and that the theory has been formulated only to explain the symptoms of iodism. Iodides have been found in the nasal secretion, saliva and perspiration, but no free iodine.

The central nervous system and the circulation scarcely seem to be affected by iodides. Very large quantities of potassic iodide injected into a vein are found to weaken and paralyze the heart in animals, but do not seem to be more poisonous than other potassium salts, and depression of the central nervous system may also be elicited in the same way by the potassium action. Barbera states that very large quantities of iodides paralyze the depressor nerve terminations in the medulla oblongata and weaken the peripheral inhibitory mechanism of the heart, while Hunt found the accelerator fibres less easily fatigued after iodide. The metabolism of the body seems little affected by iodides in most cases, but a further examination of the excretions of patients who lose weight under the treatment is desirable. Fatty degeneration of the liver is stated to occur in some animals. The action of the iodides in therapeutics has been ascribed by some authors to their rendering the movement of the leucocytes (diapedesis) more active, but no satisfactory evidence has been adduced in support of this. Solutions of iodide of sodium are found to be more poisonous to muscle, cilia and unicellular organisms exposed to them than are similar solutions of the chloride or bromide, so that the iodide ion appears to be more fatal to protoplasm than the bromide and chloride ion, while it is less poisonous than the fluoride. In the frog stiffness and awkwardness in the movements are elicited by comparatively small doses of iodide of sodium and these symptoms have been shown to be due to rigor mortis occurring in the muscles.

PREPARATIONS.

POTASSII IODIDUM (U. S. P., B. P.) (KI), 0.1–1.3 G. (2–20 grs.).
SODII IODIDUM (U. S. P., B. P.) (NaI), 0.1–1.3 G. (2–20 grs.).

0.1 - 1.3 G
2 - 20 gr

Iodides colorless or yel crystals, sol in H_2O. KI esp. Tertiary syph. up to 5 G per diem. In bones ulcers, brain gummata etc. Of value in diseases, not syphilis, but where patient syphilitic (neuralgia, rheumatism). Thyroid better in goitre & obesity.

1/2 cc *Acidum Hydriodicum Dilutum* (U. S. P.), 10 per cent. 0.5 c.c. (8 mins.).

4 cc *Syrupus Acidi Hydriodici* (U. S. P.), a syrup containing about 1 per cent. by weight of hydriodic acid. 4 c.c. (1 fl. dr.).

The iodides form colorless crystals when pure, a yellowish tint indicating the presence of free iodine. They are very soluble in water, less so in alcohol, and are always prescribed in watery solutions, and often along with carbonates of soda or potash, in order to prevent decomposition as far as possible. The iodide of potassium is the one most frequently used and is less liable to contain free iodine than the others, but iodide of sodium is preferred by some; the dose often has to be much increased beyond that given above. The iodide of ammonium is said to be more liable to cause skin eruptions and disturbance of the digestion than the others. Some iodide effects may also be obtained by the use of iodide of lead or mercury, but here they are complicated by the action of the metal, and these will be discussed along with the other salts of lead and mercury. The external application of iodides is not attended by any general effect, though some irritation may be induced by iodine being liberated by the decomposition of the fats; small quantities of iodine are absorbed and changed to iodides in the tissues.

Therapeutic Uses.—The iodides are used very extensively in the treatment of tertiary syphilis, in which they have proved invaluable. They have also been administered in the earlier stages of the disease, but have proved to be of little service here. In syphilitic bone disease and ulcers, and in the gummata of the brain and other internal organs, however, a remarkable improvement very often occurs after the iodide treatment has been adopted. The iodide of potassium or of sodium is almost invariably used, and is given in as large doses as the patient can bear, often up to 5 G. (75 grs.) daily. In the beginning of the tertiary manifestations the iodide is often prescribed along with mercury, and this combination is found more efficient than the iodide alone. No complete explanation of the action of the iodides in syphilis has been given, but it seems probable that they act as a specific poison to the organism of syphilis. In particular, the relation of the iodides and mercury in this disease requires elucidation.

In many diseases which are not directly attributable to syphilis, but in which there is a history of syphilis, iodides are of value; thus, neuralgia and other nervous disturbances are often relieved by them in persons of a syphilitic taint, and in fact, improvement is often observed in the most diverse conditions in persons who have formerly suffered from this complaint.

Another series of symptoms or of diseases which is often treated with iodides is rheumatism in its various manifestations. The treatment is of little value in acute rheumatism, and in fact, often fails in the chronic disease, but is occasionally attended with improvement, although the exact conditions in which this occurs are still unknown.

The iodides have long enjoyed some reputation in the treatment of goitre, but the thyroid extract has proved much superior to them and promises to supplant them entirely, as their effects are due to their action on the thyroid secretion. The same may be said regarding their use in obesity, which was found to be successful in some cases, presumably of thyroid insufficiency. In normal persons and animals

Resolves syph. gummata, but not non-syph. sclerosis or cirrhosis
In expectorant mixtures to liquefy secretion. In chronic Pb or Hg poisoning
In malingering – Cl water + starch paste to urine = blue.

it is often found that iodides rather tend to increase than to decrease the weight.

Some skin eruptions have been found to be benefited by the iodide treatment even when no suspicion of syphilis could be entertained. (Compare thyroid extract.)

The success attending the treatment of goitre with iodides seems to have been the basis of their use in cases of enlarged lymphatic glands, scrofula and lupus, but here the results are very doubtful, although some authorities allege that the iodide treatment is of value. There is a general consensus of opinion that the old treatment of malignant tumors, such as cancer and sarcoma, with iodides is hopeless.

These salts are sometimes credited with promoting the absorption of serous effusions, and the removal of hypertrophy of connective tissue in the body, as in the various forms of sclerosis and cirrhosis. Their effect in removing the syphilitic gumma was evidently the origin of their use here, but while the resolution of gummata under the iodides is beyond question, no satisfactory evidence of improvement in these non-syphilitic affections is available.

Aneurism and arteriosclerosis have often been treated with iodide, and improvement was undoubtedly observed in some cases, in which there was probably a syphilitic taint; but there seems no reason to suppose that the iodides have any special action on the vessels apart from their antisyphilitic action, for no change in the heart, pulse or blood-pressure can be observed even after prolonged treatment.

Iodides are often prescribed along with other remedies in expectorant mixtures, the object being to render the bronchial mucus more watery and less tenacious, and thus to facilitate its removal. In some cases of asthma they have been found of value, perhaps from the same action.

Iodide of potassium is generally prescribed in chronic poisoning from lead or mercury, and is believed to hasten the elimination of these metals, although it has not been shown that it is of more value here than other salts, such as the chlorides and bromides. The belief in the efficacy of the iodides in mercury poisoning has suggested that they act in tertiary syphilis only by aiding in the elimination of the mercury stored in the tissues from the treatment of the earlier stages, but this is incorrect, for the iodides are of value in cases of tertiary syphilis in which mercury has not been previously used.

Finally, iodide of potassium is sometimes added to other drugs in cases of malingering, or in which it is suspected that the patient is not taking the remedy as directed. If the iodide is swallowed it can be detected in the urine by the addition of a few drops of chlorine water and of starch solution, which assumes the well-known blue color.

Iodides have to be used with care in cases of pulmonary phthisis, in which they often increase the cough and expectoration, and in some cases, it is alleged, cause hæmoptysis. Children have sometimes been found to suffer with iodism from being nursed by a person under iodide treatment.

Iodine a skin irritant – forms iodides & protein comp. Dark brown. heat itching. Blistering & even corrosion

Iodism very often proves a disagreeable accompaniment of the treatment, and is sometimes so severe as to preclude the use of the salts, so that many attempts have been made to discover some expedient by which these symptoms may be avoided. Most of these were based on the view that iodism arises from the action of nitrites in an acid medium, but doubt may be entertained as to the validity of this hypothesis, and there can be little question of the inefficiency of sulfanilic acid and alkali carbonate treatment in cases of iodism. There has been a tendency recently to ascribe the symptoms to the tissues being flooded with large quantities of iodide, which are necessary on account of the rapid excretion, and this has led to the introduction of various iodine compounds, which are slowly formed to iodides in the tissues (see *Iodipin, Sajodin,* p. 517). These seem to have some iodide effects, but in grave cases recourse should be had to the older and more reliable iodides of the alkalies.

The cutaneous eruptions are said to be less liable to occur when the skin is kept scrupulously clean by frequent bathing.

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VI. IODINE.

Iodine possesses a local irritant action similar to, though less intense, than that of chlorine and bromine. It is much less volatile, and therefore comes into contact with the tissues more slowly than these, but the chemical change is analogous, and iodides and protein compounds result.

Action.—When applied to the **Skin,** it dyes it a yellow-brown or dark brown color, and acts as an irritant, producing a sensation of heat and itching. In very concentrated solution or in the solid form it may cause blistering or even corrosion, but it acts much more slowly than most other irritants, and at the same time the irritation is more prolonged. It penetrates into the deeper layers of the skin, and small quantities are absorbed.

The **Mucous Membranes** are more strongly affected by contact with it; thus when its vapor is inhaled for some time, smarting, swelling

On m.m. smarting swelling, increased secretion of nasal m-m etc as in iodism. Gastric & intestinal acute infl. Absorbed as iodides eliminated as such by kidneys, saliva, perspiration etc. HI in stomach — gives thyroid more I for secretion. Int = iodism usually + oedema of larynx

and increased secretion is caused in the nasal mucous membrane, conjunctiva, throat and lower respiratory passages, resembling exactly the symptoms known as iodism. In the stomach small quantities may cause slight irritation and improved appetite, but as a general rule nausea, discomfort and vomiting follow its administration in any save the most minute doses, and occasionally diarrhœa has been observed after it from irritation of the bowel. In cases of poisoning, the irritation of the alimentary canal may prove fatal by inducing collapse and failure of the heart and respiration, and iodine may be recognized in the vomited matter and in the stools.

Solutions of iodine **Injected Subcutaneously** or into tumors or cysts, a common method of treatment formerly, cause intense pain and irritation which may induce collapse and which have been followed in some instances by suppuration and gangrene.

Iodine is **Absorbed** in the form of iodides, and perhaps in a combination with proteins. The ordinary iodalbuminate obtained by adding iodine to albumin is a very loose compound, and is easily decomposed by dialysis, or by heating it to the coagulation point of the albumin, when the iodine is obtained free or in combination with alkalies. Several stronger and more definite compounds have been formed recently, and it is not impossible that the iodalbuminate formed in the process of absorption is of a similar nature. In combination with albumin, iodine fails to give the starch reaction. Its **Fate in the Body** is precisely similar to that of the iodides—it is excreted in the form of iodides, chiefly by the kidneys, to a less extent in the saliva, perspiration, milk and secretions of the respiratory passages. It also occurs in the stomach, into which it appears to be excreted as hydriodic acid; free iodine has been detected here in both man and animals, and is probably formed by the decomposition of the acid. In the normal organism iodine is contained in considerable quantity in the thyroid gland in the form of a protein compound, thyreoglobulin, and in many cases the administration of iodine leads to an increase in the formation of this substance, perhaps by actually stimulating the secretory cells of the thyroid, but more probably by affording them a larger amount of a necessary constituent of their secretion than is obtained in ordinary food.

Small quantities of iodine may be given internally to many persons without eliciting any symptoms except those which are clearly due to the local action. Repeated doses, however, sometimes cause symptoms resembling those observed after iodides **(Iodism)**, although these have been much less often induced by iodine, which is comparatively seldom administered internally. Skin affections seem to be extremely rare and irritation of the respiratory tract is seen less often after iodine than after the iodides, but œdema of the larynx has been observed, and in rare cases cough and the expectoration of a watery secretion tinged with blood. Anuria and albuminuria have occurred in a few instances. Many other symptoms which have been observed under iodine treatment obviously arise from the formation of iodothy-

Excess of iodothyroidin (as in goitre) = fever, loss of flesh, shrinkage of thyroid mammae, testes, nervous v. Iodine int. acts on thyroid. Iodides irritate skin & mem. Danger of poisoning when I into cysts

Tincture = 7% - 0.1cc

Lugols = 5% I + 10% KI - 0.2cc

rin in excess by the thyroid gland, and are especially noticeable in goitre. Among these are fever with loss of flesh and shrinking in size of the thyroid, mammæ and testes, acceleration of the pulse and a curious nervous condition in which the patients become restless, anxious and irritable, and suffer from sleeplessness and often from tremor, which sometimes simulates chorea.

The symptoms induced by iodine after absorption thus resemble in general features those following the use of the iodides, but while the latter tend to cause irritation of the skin and respiratory tract, the chief effects of iodine after absorption are due to its action on the thyroid gland, the effects on the skin and mucous membranes being less prominent.

The effects of iodine on the **Metabolism** are still a matter of dispute, some authors finding no alteration, while others state that the excretion of urea is increased. They probably differ in different individuals according to the condition of the thyroid gland.

Some **Cases of Poisoning** from the injection of large quantities of iodine into cysts have been recorded. In Rose's well-known case, the chief symptoms were thirst, constant vomiting, the vomited matter containing iodine, cyanosis and coldness of the skin, a small, weak pulse, anuria and skin eruptions after a few days; and death occurred on the tenth day. In such cases of poisoning in man the mucous membrane of the stomach and intestine has been found swollen and loosened, and in animals fatty degeneration of the liver, heart and kidney has been described.

Injected into the veins of animals, iodine causes œdema of the lungs, which v. Zeissl considers to be due in part to changes in the left ventricle, in part to contraction of the pulmonary arterioles.

The muscles of the frog are thrown into a state of rigor by iodine in the same way as by the iodides.

Iodine dissolves the red blood corpuscles when it is brought in contact with them outside the body, and forms a combination with hæmoglobin.

PREPARATIONS.

Iodum (U. S. P., B. P.), iodine, is not used in therapeutics.

7% 0.1cc *Tinctura Iodi* (U. S. P.), 7 per cent., 0.1 c.c. (1½ mins.).

Tinctura Iodi (B. P.), 2½ per cent., 2–5 mins.

Lugols 0.2cc *Liquor Iodi Compositus* (U. S. P.), Lugol's Solution, contains 5 per cent. dissolved in 10 per cent. potassium iodide solution. 0.2 c.c. (3 mins.).

Unguentum Iodi (U. S. P., B. P.), 4 per cent.

Liquor Iodi Fortis (B. P.), Iodine Liniment, about 14 per cent.

Sulphuris Iodidum (U. S. P., B. P.) is a mixture of iodine and sulphur, part of which may be in chemical combination. It resembles iodine in its action on the skin.

Unguentum Sulphuris Iodidi (B. P.).

The compound solution of iodine is the preparation best fitted for internal use, although the tincture is also employed. Both should be given after meals and as far as possible diluted with demulcent preparations, in order to avoid irritation of the stomach.

For injection into cysts or tumors the compound liquid is also the best preparation, as it is less irritant than the tincture.

Chiefly supplanted by iodides in syph., tb of glands, bones, etc., by thyroid in Goitre. Revival but as comb. with proteins Eigon, Iodolen & fats Iodipin. Changed to iodides in ali. canal & tissues. Elimination by weeks. Skin paint for chron. infl. as tb. glands & joint disease. Only a mild & enduring skin irritant. N.B.- for injection into cysts.

The tincture, ointment, the strong solution (B. P.) and the sulphur iodide preparation may be used for external application.

Therapeutic Uses.—Iodine has been used internally in a variety of chronic conditions, such as syphilis and goitre, and in tubercular disease of the glands, bones and other organs, but it has been almost entirely superseded by the iodides, and in goitre by the thyroid preparations.

The internal use of iodine has undergone a revival quite recently, but instead of the older solutions, new preparations have been introduced, such as the combinations with proteins (*Eigon, Iodolen*), or with fats (*Iodipin*), or with other organic bodies (*Sajodin*). These owe their action to the formation of iodides in the alimentary tract and tissues, and iodides may be detected in the urine soon after their administration. The decomposition proceeds slowly, however, and the iodide reaction is given by the urine for weeks after one administration. Iodipin has also been given hypodermically.

Iodine has been applied locally by painting on the skin in a variety of chronic inflammatory processes, such as tubercular glands, pleuritic effusion and tubercular or rheumatic joint disease. Its action here consists simply of a mild lasting irritation of the skin, which induces some congestion in the subcutaneous tissues and may thus aid in the absorption of exudates in them and may also influence the deeper lying tissues and organs in the same way as other irritants (see page 81). There is, however, nothing specific in its action, and it differs from the other skin irritants only in being milder in action and more enduring in its effects. It seems unlikely that the small quantity absorbed can have any appreciable action. Some benefit often follows from this use of iodine in chronic inflammations, but there is no question that it is very often applied where more active surgical measures are really required.

Iodine has been very frequently injected into cysts in order to induce inflammation and adhesion of their walls, and thus to obliterate the cavity. But the progress of surgery has reduced its use for this purpose and it promises to pass into desuetude.

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VII. IODOFORM.

A number of iodine compounds have been introduced into therapeutics as applications to wounded surfaces. The most widely known of these is Iodoform (CHI_3), which corresponds in its chemical structure to chloroform, and forms a yellow, crystalline, insoluble powder with an intensely disagreeable odor. It has been used very extensively in surgery and has given rise to poisoning in a number of cases.

odoform to wounds - possible poisoning - Sym ✓. In mild poison = unpleasant taste and odor, nausea, headache ✓. Thyroid secretion increased n fatal case = fatty deg. of liver, kid; irritation + deg. of ali canal epithelium

Symptoms.—The symptoms of iodoform intoxication in man generally set in with anxiety, general depression and discomfort. The patient becomes sleepless and restless, complains of giddiness and headache and often of the taste and odor of iodoform in the mouth and nose. The pulse is generally greatly accelerated, and a rise of temperature is said to have occurred in some cases in which no septic poisoning could be found to account for it. The depression deepens into true melancholia accompanied by hallucinations, the patient often suffering from the illusion of persecution, which may induce him to attempt suicide. As a general rule this melancholia is followed by attacks of violent delirium and mania, lasting for hours or days, and in fatal cases, by collapse and death. In other cases the condition has passed into permanent insanity and dementia. A rarer result of the absorption of iodoform is deep sleep passing into stupor and collapse without any symptoms of cerebral excitement.

In milder cases of poisoning the patient suffers only from the unpleasant taste and odor, from headache and not infrequently from nausea and vomiting.

In the dog and cat iodoform generally causes deep sleep and stupor, with lessened excitability of the spinal cord and of the motor areas of the brain. In the frog it paralyzes the central nervous system and the heart without eliciting any symptoms of excitement. No narcosis is observed in the rabbit even after fatal doses.

The symptoms most characteristic of iodoform poisoning—those of delirium and mania—are evidently due to cerebral disturbance, but nothing is known as to the nature of the changes in the brain. No other poison elicits these symptoms in the same intensity and of equal duration, and no similar effects have been met with in animals.

Acceleration of the heart has been noted in many cases of poisoning. After prolonged administration albuminuria is often observed in animals, and the thyroid secretion has been found to be increased to a very considerable extent by iodoform, as by other bodies which free iodine in the tissues.

After fatal iodoform poisoning in man and animals, the liver, kidney, heart and muscles are generally found to have undergone fatty degeneration. In addition, irritation of the gastric and intestinal mucous membrane has been observed, and the epithelial cells are often degenerated. Ecchymoses occur beneath the endocardium, in the kidney and elsewhere, and congestion of the meninges is described.

Absorption and Excretion.—Iodoform is readily decomposed in the presence of alkaline fluids and in protein solutions, and some decomposition undoubtedly takes place in wounds; the iodine liberated combines with the alkalies of the fluids to form iodides, for these have been shown to be present, and iodalbuminates are presumably formed in the same way as by free iodine. Some of the iodoform is perhaps absorbed unchanged. After iodoform absorption, iodine has been shown to be present in the saliva, perspiration and bronchial secretion, as after the ingestion of iodine or iodides; but it is chiefly excreted in

Chiefly → in urine as iodides. Some broken into I also I + K = KI
Tissues retain iodides tenaciously for over 1 month esp. in renal disease!
Complex action: factors: iodoform, I, iodides, increased thyroid secretion.
Little local skin effect. Of little value as antiseptic — what
little action - due to liberation of free I or forming a crust

the urine in the form of iodides. The tissues apparently retain it very tenaciously, for iodides have been found in the urine for more than a month after the administration of iodoform.

In considering the symptoms of iodoform intoxication, it must be recognized, therefore, that a very complex condition is present. Some iodoform may circulate in the blood unchanged and give rise to the cerebral symptoms. Other symptoms are due to the presence of iodine and iodides in the blood and tissues. Lastly, the acceleration of the heart and some other symptoms are due to abnormal activity of the thyroid secretory cells. It is possible that the cerebral symptoms may arise from the thyroid gland through the action of iodoform on it, but this has not been demonstrated.

Poisoning with iodoform is much more liable to occur in adults than in children. Serious symptoms, especially mental symptoms, are often developed only after somewhat prolonged administration, but in renal disease the iodoform products are excreted more slowly than usual, and are liable to accumulate in the tissues, so that it is to be used with caution.

Iodoform has no marked **Local Action** on the skin or mucous membranes. When applied to wounded surfaces it sometimes causes some irritation in the neighborhood and even exanthemata, but these are rare, and appear to occur only in persons predisposed to cutaneous disease. It seems to have some anæsthetic action, when applied in large quantity to wounded surfaces. Iodoform was at first applied to wounds in the belief that its **Antiseptic** properties were equal to or even exceeded those of carbolic acid. It has been shown, however, that it possesses little or no influence on the cultures of most of the pathogenic microbes, for the spores often develop as rapidly after having been subjected to iodoform as in the control cultures. It has therefore been suggested that while iodoform in itself possesses no antiseptic virtues, the iodine formed from it in the wound may retard the growth of septic germs. And in regard to this point bacteriologists are not agreed, for while several investigations tend to show that microbes drawn from wounds under iodoform treatment are not retarded or weakened in their development, other experiments indicate that the virulence of some germs is reduced. Some of the advocates of the iodoform treatment therefore ascribe its results to this slight antiseptic action of the iodine, while others suppose that it diminishes the secretion of the wounded surface and thus affords a less suitable medium for the growth of the germs; in this relation it may be mentioned that Binz found the emigration of the leucocytes from the blood vessels hindered by the local application of iodoform. Finally iodoform may retard the growth of microbes to some extent by forming a crust over the wounded surface, and mechanically preventing them from penetrating to it.

The intensely disagreeable odor of iodoform and the considerable number of cases of poisoning noted under its use have led to the introduction of numerous substitutes in the last ten years. Some of these

Substitutes of little value. Iodoformum insol. in H_2O sol in alcohol, oils, glycerine. In application to wounds, skin diseases & burns, profuse secreting granulations & slow healing abscesses; in syph ulcers

have been shown to be practically worthless and have been discarded, while the greater number are apparently used more or less widely, but accurate data as to their value cannot be obtained. None of them seem to be very poisonous, and in most of them the iodine of the molecule is not liberated in the wound or tissues. It is of course impossible to state how far they are capable of replacing iodoform, as long as their exact action in wounds is unknown.

The first of these substitutes was *iodol* or tetraiodpyrrol (C_4I_4NH), which has no odor or taste, is insoluble in water, but is absorbed from mucous surfaces and from wounds. It is decomposed in the tissues, and leads to the excretion of iodides in the urine, and in very large doses gives rise to symptoms in animals resembling those produced by iodoform. Others are *aristol* or dithymol-diiodide ($(C_6H_2CH_3C_3H_7OI)_2$), and the *sozoiodolates* of potassium, sodium, mercury and zinc. Sozoiodolic acid is phenol-sulphonic acid in which two atoms of hydrogen have been substituted by two atoms of iodine ($C_6H_2I_2HOSO_2OH$). Iodine compounds of phenol-phthalein are known by the trade names of *nosophen, antinosine* and *eudoxine.* Triiodocresol is known as *losophan,* while *europhen* is a more complex combination of cresol and iodine; *loretin* and *vioform* are derivatives of quinoline containing iodine. (See also under Bismuth and Alum.) These later "substitutes" for iodoform differ entirely from it and from iodol in the fact that iodine is not liberated by the tissues; that they pass through the body unchanged, as far as the iodine is concerned, and that they are said to be entirely devoid of poisonous effects, and in fact of any action, save as local antiseptics. They are almost all phenol derivatives, and any virtues they possess may prove to be due to this fact mainly, and not to their containing iodine. They are all less used at the present time than a few years ago.

PREPARATIONS.

.03-.25 **Iodoformum** (U. S. P., B. P.), iodoform (CHI_3), forms small, lemon-colored crystals, possessing a very penetrating, persistent and disagreeable odor and taste, practically insoluble in water, soluble in alcohol, ether, fixed oils, glycerin, etc. 0.03–0.25 G. (½–4 grs.), in pills or capsules.

10% UNGUENTUM IODOFORMI (U. S. P., B. P.), contains 10 per cent. iodoform.

Iodolum (U. S. P.), $C_4I_4 \cdot NH$, a light grayish-brown crystalline powder, tasteless, odorless, insoluble in water. Dose, 0.25 G. (4 grs.).

Thymolis Iodidum (U. S. P.), *Aristol* ($(C_6H_2 \cdot CH_3 \cdot C_3H_7 \cdot OI)_2$), a yellowish-brown powder resembling iodol in its properties.

The *Sozoiodolate* of potassium is slightly soluble in water, the sodium and zinc salts more soluble. Mercury forms an insoluble salt which may be dissolved by the addition of sodium chloride.

Therapeutic Uses.—Iodoform has been used to a very limited extent internally in the treatment of syphilis, and as an intestinal disinfectant. It is chiefly employed in surgical treatment as an application to wounds, skin diseases and burns. In granulating surfaces with a profuse secretion, and in slowly healing abscess cavities, it seems to be especially valuable. It may be applied as a dusting powder, as an ointment, or in gauze or bandages saturated with it. It has been shown that it has very weak antiseptic properties, and many surgeons take the precaution of disinfecting the powder before applying it, and use it for its effect on the tissues of the wound and not for its effects on the germs. Applied in ordinary quantity to small surfaces it seems to be a perfectly safe remedy, cases of poisoning occurring only when large cavities are plugged with it, or when it is applied to very large absorbent surfaces. Many attempts have been made to disguise its disagreeable odor, but have been attended with only moderate success. Among the best of the many perfumes suggested for this purpose is cumarin, which is contained in large quantity in the Tonka bean.

Iodoform has been credited with some specific action in tubercular disease, but has proved almost inert towards the bacillus. The favorable results in the local treatment of tubercular abscesses, laryngeal ulcers and similar conditions may with greater probability be attributed to its action on the granulation tissue. In syphilitic ulcers and chancres, iodoform has been used very largely and with good effects.

Iodol may be used as a substitute for iodoform, and is applied in the same way. The sozoiodolates are used as powders or ointments, or in the case of the sodium, zinc and mercury salts, in solution. The last is poisonous, and is comparable to corrosive sublimate in its effects.

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VIII. THYROID GLAND.

The treatment of certain diseases by the administration of thyroid gland and its extracts is one of the most satisfactory examples of rational therapeutic progress, and the steps which led to its adoption may therefore be briefly mentioned. In 1882–3, Kocher and Reverdin published observations made on patients whose thyroids had been totally extirpated, and who had subsequently presented a series of symptoms to which these observers gave the name of cachexia thyreopriva. They pointed out that this condition resembled in many of its features myxœdema, a disease discovered by Gull some years before and associated with atrophy of the thyroid gland. These observations were confirmed by a number of authors, who removed the thyroids from animals, and found a cachexia appear in them. The next advance was the discovery that these symptoms in animals could be removed, or at any rate ameliorated, by grafting pieces of thyroid in the peritoneal cavity or subcutaneous tissue. Horsley suggested that myxœdema should be treated in the same way, and Murray soon afterwards introduced the treatment of this disease by the subcutaneous injection of thyroid juice. Even in his first case, the results were

Injection of juice or by mouth for [illegible] [illegible] thyroidectomy, myxoedema, or thyroid disease. In colloid of glands as thyreoglobulin (globulin + some I). I not absolutely essential for gland activity.

eminently satisfactory, but it was soon found that the same results could be obtained by administration by the stomach, and a large number of cases have now been recorded in which very favorable results, or even the complete disappearance of the symptoms has followed this medication. These include not only myxœdematous patients, but also cases in which the thyroid was removed by surgical operation, or where its disease gave rise to symptoms. That the favorable results are due to the treatment is proved conclusively by the return of the symptoms when it is abandoned.

The effect of the thyroid extract could be explained only by the presence of some chemical principle, for the preparation of course contained no living cells. In the last few years, numerous researches have been carried out with the object of isolating this principle.[1] It is found in the colloid contents of the gland follicles in the form of a globulin, *thyreoglobulin,* which may be extracted from the colloid and gives the ordinary protein reactions, but is characterized by containing a small percentage of iodine; Baumann's detection of this element in the thyroid gland was the first intimation that it existed in the tissues of the higher animals and man. Thyreoglobulin is not completely saturated with iodine, for it forms a higher combination with it in the test-tube, but then loses its specific action on the animal organism. When it is subjected to acids or to artificial digestion it undergoes hydrolysis like other proteins, and among the products Baumann found an insoluble non-protein body containing practically all the iodine of the gland, which he named *iodothyrin;* this does not seem to be a definite substance, however, but is a mixture of peptides combined with iodine. Hunt has shown that the iodine compound is not the only active principle in the gland, for thyroids containing no iodine have a certain degree of activity, though this is greatly inferior to that of glands containing iodine. He suggests that the thyreoglobulin is therapeutically active even when it contains no iodine, but that when it is combined with iodine it is much increased in power. In fact the amount of iodine in the gland may be inferred fairly accurately by the changes induced by its administration. In the gland there may exist thyreoglobulin in very different degrees of combination with iodine, and the products of hydrolysis accordingly contain different iodine compounds. At present the efficiency of the gland cannot be measured by the amount of any of the compounds, but only by that of the iodine itself, and this varies a good deal in different animals and in different individuals of the same species. For example, less is found in the glands of children than in adults, and after middle age it lessens again. Meat diet diminishes the amount of iodine, either because it makes greater demands on the supply, or because too little iodine is ingested in the food. Vegetable foods, especially those containing much iodine, such as beetroot and the marine algæ, increase the iodine of the thyroid gland. Iodine

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[1] **No attempt is made to follow the chronological order of these researches.**

I a way to estimate glands function. less in young & very old. less when
little in diet. Iodothyrin & thyreoglobulin the active principles of thy gla
Many give symp. in normal persons – Heart acceleration – etc

given medicinally also augments it, and not only iodine itself, but various combinations, such as iodoform and iodides.

Thyreoglobulin and iodothyrin induce the same effects as the extract both in myxœdema and goitre in man and in excision of the thyroid in animals. This has been disputed until recently, owing to the fact that in many cases the parathyroid glands have been removed along with the thyroid in animal experiments. Now the removal of the parathyroids in dogs (on which the experiments have generally been performed) leads to a series of symptoms arising from the central nervous system, and these are not affected by thyroid medication. When the thyroid alone is removed, the symptoms are relieved by iodothyrin, thyreoglobulin, or thyroid extract, and the two first therefore represent the whole therapeutic virtues of thyroid extract, although it is possible that the gland may have other functions than secretion. Thyroid preparations are thus used to replace the secretion of the thyroid gland, when it is deficient from any cause. The function of the thyroid gland is still very obscure, however, although it is now certain that it is of great importance in the metabolism, as is clearly shown by the disastrous results of its removal or atrophy. The results of the injection of the thyroid extract have also thrown much light on the working of this mysterious organ.

Action.—The thyroid extracts and iodothyrin seem to be devoid of effect in many normal animals and patients, unless when given in enormous quantities. In others they cause some unpleasant symptoms, which occur more especially in myxœdema and goitre. These symptoms are partly subjective and indefinite, such as headache, wandering pains, or general weakness, while others are evidently due to circulatory changes, and consist of a feeling of fullness and congestion of the head, palpitation of the heart, and acceleration, sometimes weakness, of the pulse. Tremors in the arms and legs point to changes in the central nervous system, while loss of appetite and diarrhœa indicate that the alimentary canal is not exempt from its influence. Perspiration is often complained of, especially in myxœdema, and a rise of temperature also occurs not infrequently.

In normal animals thyroid extract injected intravenously in large quantities generally accelerates the heart and lowers the blood-pressure somewhat, and even when given by the mouth repeatedly for several days, it causes some acceleration. This acceleration of the heart has been attributed by some investigators to stimulation of the accelerator centre, by others to direct action on the heart; it does not seem to be due to any changes in the inhibitory apparatus.

Loss of flesh and thirst have been observed, even when the appetite is good and sufficient food and water are supplied. The urine is uniformly increased in amount. A number of observers have found that the continued administration to animals of thyroid preparations in large amounts leads to diarrhœa, muscular weakness, especially in the hind extremities, emaciation, gastro-enteritis, nephritis, and fatty degeneration of various organs. In other instances no such symptoms

Overdose in man = sym. of exophthalmic goitre or Graves disease. Common results = acceleration of heart & loss of wt: Increase N in urine due to protein destruction. Fats & c.h. more rapidly oxidised - More O + CO exchanged esp in myxoedema. Diuresis: due to increased excretion of urea.

have been elicited, the animals remaining perfectly normal after prolonged treatment.

Some of the symptoms induced in man by an overdose of thyroid resemble those seen in exophthalmic goitre or Graves' (Basedow's) disease, and exophthalmos has been observed in monkeys to which large amounts of thyroid were given.

As may be gathered from the above, great discrepancies occur in the accounts of the effects of thyroid on normal animals. The acceleration of the heart and the fall in weight seem to be the most common results.

The effects of thyroid extract on the **Metabolism** have been repeatedly examined, with very uniform results. One of the most striking features in many individuals is the rapid loss of weight, which often amounts to several pounds per week. Another is the increase in the amount of nitrogen in the urine, which occurs both in goitre and myxœdema, and very often in apparently normal persons. More nitrogen is excreted in the urine frequently than is taken in the food, that is to say, the treatment leads to the destruction of the proteins of the tissues. If more nitrogenous food be given, however, this may be arrested, and in fact if large quantities of meat be taken, less nitrogen may be excreted than is taken in the food, so that although the patient is losing in weight, he may be actually increasing in nitrogenous tissue. If, on the other hand, a patient has been put in nitrogenous equilibrium, and then under thyroid medication excretes more nitrogen than he ingests, this excessive tissue waste is not stayed by increased carbohydrates and fats; that is, the carbohydrates and fats cannot replace nitrogenous food to the same extent as in normal individuals. Thyroid has thus a specific effect in increasing the waste of the proteins of the body. But this increased waste of the proteins only accounts for about one-sixth of the loss of weight, the other five-sixths being evidently due to the more rapid oxidation of fats and the removal of fluid from the body.[1] The more rapid oxidation is further evidenced by the increased amount of oxygen absorbed and of carbonic acid exhaled by the lungs in cases of myxœdema and sometimes in obesity and goitre treated with the extract. The removal of fluid from the body, perhaps the most potent factor in reducing the weight in these cases, is shown by diuresis, which occurs in myxœdema especially, but also in obesity. This diuresis has been ascribed to some specific action on the kidney, or to the changes in the circulation, but may perhaps be due to the increased excretion of urea and other urinary substances. That the kidney is acted on in some cases is shown by the occasional appearance of albumin in the urine of patients

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[1] Schöndorff states that in nitrogenous equilibrium the oxidation of the fats is increased before the proteins of the body are attacked, but when the fat destruction has reached a certain point, the protein waste is also increased. The early augmentation of the nitrogen of the urine does not indicate an acceleration of the protein metabolism, but is due to the removal of urea and other products, which have been formed in the tissues before the administration of the remedy, but which are now excreted through the increased activity of the kidneys.

Phosphates also increased. Glycosuria not uncommon. Children show few sym.
Adults lose flesh, & → thyroidism, esp in myxoedematous. In Graves' disease
the symptoms aggravated.

treated with thyroid preparations. The phosphates excreted are increased in the same ratio as the nitrogen, and the increase is obviously due to the same cause, augmented protein waste.

In some cases sugar has been found in the urine after thyroid treatment, and in a considerable percentage of persons it seems to cause a tendency to glycosuria, as is shown by the appearance of sugar in the urine after the ingestion of large quantities of sugar, which would normally be oxidized in the tissues. There is further evidence that thyroid extract influences the carbohydrate metabolism, but no satisfactory statement is available at present. The uric acid excretion does not seem to be materially affected by thyroid treatment.

After thyroid preparations have been administered, iodine is found in the urine in the form of iodides, so that the iodine compound is evidently decomposed, at any rate in part, in the body. The rest of the iodine is taken up by the thyroid gland.

Hunt has recently made the observation that the administration of thyroid extract diminishes the susceptibility of mice to acetonitril (CH_3CN), a poison which seems to act by freeing prussic acid in the tissues, and the degree of protection afforded varies directly with the amount of iodine of the gland. On the other hand, it increases the susceptibility of rats to the same poison, and morphine is more toxic to both mice and rats when they have been treated with thyroid for some time previously. The presence of even very minute quantities of thyroid extract may be demonstrated by feeding these animals with it and testing their resistance to these poisons.

In regard to their reaction to thyroid medication, individuals vary considerably, for many are scarcely affected by it in any way, and this is particularly true of children, while others lose weight rapidly, and under larger doses show symptoms of poisoning (thyroidism). These seem to be more easily elicited in goitre and myxœdema than in ordinary cases. On the other hand, in Graves' disease the symptoms are generally aggravated by thyroid treatment. There is every reason to believe that this condition is due to the excessive production of thyroid secretion, and Hunt has succeeded in demonstrating its presence in the blood in one case of the disease.

The fact that "thyroidism" occurs more frequently in myxœdematous than in normal persons seems difficult of explanation, and it has been suggested that the symptoms are due, not to the extract itself, but to the products of its action. It may be supposed that in myxœdema a large amount of some substance accumulates in the tissues, because the secretion is not present in sufficient quantity to decompose it, and that when the thyroid treatment is commenced, the body is flooded with the products of decomposition and these give rise to symptoms. In normal persons, on the other hand, there is no such accumulation, and the extract therefore induces no symptoms until it is given in such quantity as to induce intoxication itself. In Graves' disease thyroid extract would, of course, tend to aggravate the symptoms, if these are due to its excessive production. Until more is learned of the action of the thyroid and of the cause of Graves' disease, however, these explanations are mere hypotheses, and they need not be entered upon further here.

Iodine, as has been stated, increases the iodine of the gland, and this explains the beneficial effects formerly seen in goitre from the application of iodine internally and locally. When iodine was efficient in those cases, and

In goitre extract useful, as it contains something besides I
Dried thyroid or extract as powders, pills, 1/2 gr of dried gland as a starter
In myxoedema beware of increased cardiac rhythm

Read margins

any considerable diminution of the gland occurred, it was often accompanied by symptoms exactly resembling those produced by large doses of the extract. Those symptoms were caused by small quantities in some patients, while much larger doses had no such effect in others—a fact which gave rise to some discussion and several erroneous theories. Sometimes the acute symptoms passed into a cachexia of very long standing. The quantity of iodine required to act in goitre is much greater than the iodine of the thyroid extract necessary, and this shows that the latter acts not merely as an iodine compound, but as the specific substance of the gland. Various iodine compounds, such as *iodalbumin* and *iodospongin* (the iodine compound of the sponge) have been shown to be practically inert in goitre.

PREPARATIONS.

0.2 - 0.6 G **THYROIDEUM SICCUM** (B. P.), **GLANDULÆ THYROIDEÆ SICCÆ** (U. S. P.), a powder prepared from the fresh ~~and healthy~~ thyroid gland of the sheep. It forms a light, dull-brown powder with a faint, meat-like odor and taste, free from any odor of putrescence. About 16 grs. represent an entire gland. Dose, 0.2–0.6 G. (3–10 grs.).

LIQUOR THYROIDEI (B. P.), a liquid prepared from the fresh and healthy thyroid gland of the sheep, and containing some phenol. A pinkish, turbid fluid, entirely free from any odor of putrescence. It ought to be freshly prepared. 6 c.c. (100 mins.) represent an entire thyroid gland (5–15 mins.).

Thyroid medication may be carried out in a number of different ways. The old method of ordering the raw or toasted gland to be taken daily may now be said to be rendered obsolete by more elegant preparations, such as dried thyroid or thyroid extract in powder form or in pills or tablets, or the liquor. These ought not to be prescribed in large quantities, ~~as they are~~ liable to undergo putrefaction unless when carefully kept; iodothyrin tablets have also been introduced, each containing 0.001 G. ($\frac{1}{60}$ gr.) or more of iodine. The dose should be small at first (*e. g.*, ½ gr. of the dried gland or 2–3 mins. of the liquor every evening for the first week of treatment) and should be gradually increased, until improvement sets in or unpleasant symptoms arise.

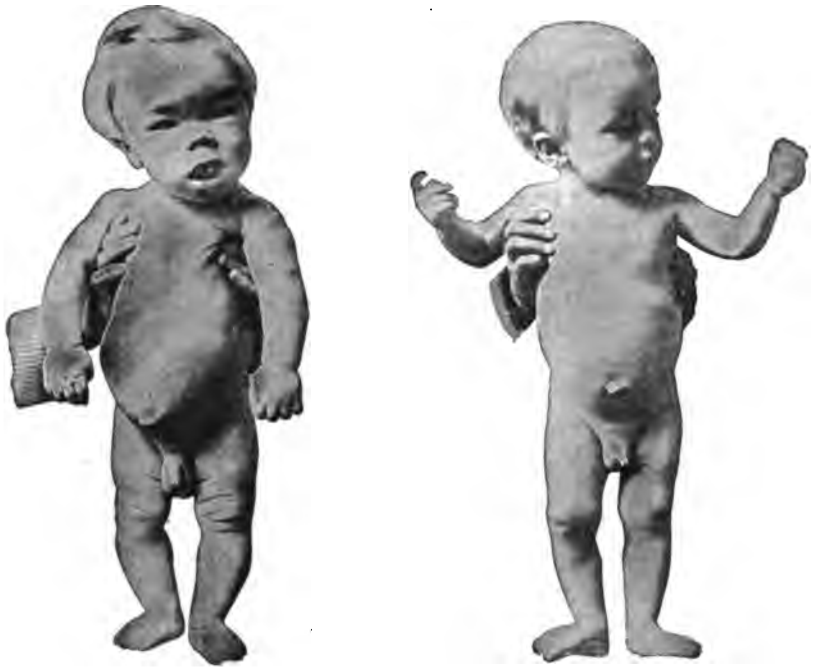
Therapeutic Uses.—Thyroid extract is not a dangerous remedy, unless in certain cases. In myxœdema, however, it should be used with care, especially if the heart is seriously affected, as the cardiac muscle may be unable to meet the requirements of the accelerated rhythm; several serious cases and one or two fatalities have already been recorded in these conditions.

Thyroid extract is useful as a substitute for the normal gland secretion in cases where the latter is wanting or deficient, as in myxœdema, cachexia thyreopriva, goitre and sporadic cretinism. In all of these the medication has to be continued for a long time, perhaps throughout life, as otherwise the patient relapses into his former condition. The decrease in weight occurring in thyroid medication suggested its use in obesity, and it has been followed by some loss of weight in a certain number of cases, especially when accompanied by proper dietetic treatment. In many instances it has had little or no effect, however, and the initial encouraging action is seldom maintained when the treatment is continued, the daily loss of weight gradually becoming smaller until it ceases altogether. The amount of fat actually destroyed seems to be trifling, Magnus-Levy estimating that about one pound disappears in ten days, which is much less than can

Not always reduces weight. Possibly dangerous: "Antifat" remedies. Improvement of brain sym in myxoedema & cretinism. Harmful in Graves' disease. Relation to thymus.

be got rid of by judicious exercise and an appropriate dietary. Besides, the continued use of thyroid in these cases is not altogether devoid of danger. Many of the antifat remedies put on the market contain thyroid extract and their continued use has led to serious symptoms in a number of cases.

FIG. 59. FIG. 60.



A case of sporadic cretinism. Fig. 59, before treatment, age 23 months, height 28 inches, circumference of the abdomen 19 inches. Fig. 60 after treatment with thyroid extract for 5½ months, height 30 inches, circumference of abdomen 15 inches. (OSLER.)

In some skin diseases, especially in psoriasis, it has been of benefit, though not by any means invariably, and in syphilis of old standing some improvement has been seen. This is probably due to the iodine contained, and not to the specific gland secretion. At the same time the peculiar combination in which the iodine is present may perhaps be more easily made use of by the economy than the ordinary inorganic preparations.

The improvement seen in the brain symptoms in myxœdema and cretinism suggested its use in other mental diseases, but the action in the former is due to its substitution for the normal secretion, and little or no effect has followed in ordinary cases of mental disease.

In Graves' disease it seems generally to be injurious. A curious relation appears to exist between thyroid and the thymus gland, for the administration of the latter is often attended by some relief in this disease.

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IX. FLUORIDES. n.s.

The fluorides present many points of difference from the other halogen salts in their chemical reactions and also in their effects in the organism.

The fluoride of sodium, which alone has been examined, possesses a powerfully irritant local action, which is seen most clearly when it is applied to the mucous membranes of the eye or of the alimentary tract. In the former it causes congestion and inflammation of the conjunctiva and opacity of the cornea, when it is applied in a two per cent. solution for some time. Small quantities induce irritation of the stomach, nausea and vomiting, and the prolonged administration leads to irritation of the intestines and diarrhœa; solutions of the fluorides are absorbed with great difficulty by the intestinal epithelium. When injected subcutaneously fluorides often induce inflammation and suppuration with necrosis.

In frogs small doses induce prolonged fibrillary contractions of the muscles throughout the body, which are due to a stimulation of the terminations of the motor nerves. Larger doses paralyze the central nervous system and eventually the motor terminations, and even the nerve fibres. The muscles lose their irritability and pass into very marked rigor, and the heart muscle is also paralyzed by large quantities.

In mammals the first symptoms are increased secretion of saliva and tears, acceleration and deepening of the respiration, followed by a condition of weakness and somnolence. Strong fibrillary tremor of the muscles then sets in with occasional stronger twitches, which eventually pass into attacks of general convulsions. In the intervals between the convulsions the animal lies in a state of profound coma. The respiration is finally arrested during an attack of convulsions, the heart continuing to beat for some time longer.

Tappeiner found a very marked fall of blood-pressure produced by sodium fluoride, and attributed it to depression of the vaso-motor centre. It may in part account for the stupor, but this indirect action is in all probability strengthened by a direct depression of the higher nervous centres. The convulsions are central in origin, while the cause of the fibrillary contractions in mammals is unknown. The respiratory centre seems to be first stimulated and then paralyzed. Muscles, nerves and other excised tissues die much sooner in solutions of sodium fluoride than in corresponding ones of the chlo-

$KClO_3$ does not increase O supply to tissues. In mouth diseases. Poisoning very variable. Salt action may give vomiting & later diuresis

ride, iodide or bromide, so that the fluoride ion must be assigned a position quite distinct from the other halogen ions in the scale of toxicity.

The fluorides absorbed from the alimentary canal are excreted by the urine, but this takes place very slowly, and much of the fluoride is stored up in the body, some in the liver and skin, but most in the bones in the form of calcium fluoride. Crystals of this very insoluble salt are found in masses in the Haversian canals, and increase the hardness and brittleness of the bones.

The prolonged administration of fluorides to animals has been found to cause weakness, loss of flesh, and irritation and ulceration of the gums.

The fluoride of sodium has considerable antiseptic power, putrefaction being delayed by the addition of one part to 500 of fluid, and one in 200 arresting completely the growth of bacteria. It has been used to a very limited extent as a surgical antiseptic.

Hydrofluoric acid is an exceedingly powerful caustic, destroying the mucous membranes wherever it comes in contact with them. It has been observed that workers in certain departments of glass factories, in which the atmosphere contains a small amount of this acid, are very seldom attacked by tuberculosis, and an attempt has been made to treat pulmonary phthisis by the inhalation of very dilute vapors. The results have not been successful, although there is no question that hydrofluoric acid is a powerful germicide.

Sodium fluorosilicate ($SiFlNa_2$) has also been used as an antiseptic in solution. It has been found to cause nausea, eructation and slowness of the pulse when swallowed.

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X. CHLORATES.

The chlorate of potassium, introduced into therapeutics on the erroneous theory that it would supply oxygen to the tissues, has been used very extensively for its effects in certain diseases of the mouth. It was supposed to be entirely devoid of poisonous properties, but was shown by Jacobi to give rise to very grave and even fatal symptoms in some instances. In such cases the symptoms are due partly to the salt-action, but chiefly to the specific effects of the chlorate ion. The chlorate of sodium induces these chlorate symptoms, and the chlorate of ammonium is said to be the most poisonous of the three. It would seem that the conditions which determine their appearance are not universally present, for very often large quantities have been taken with impunity, while in other individuals much smaller quantities have induced grave poisoning.

Symptoms.—The chlorates have a cool, saline taste, which persists for a long time owing to their being excreted in part in the saliva. Concentrated solutions may cause nausea and vomiting from their local salt-action in the stomach, and their absorption is often followed

Hardly specific poisoning on haemoglobin ([illegible]) [illegible] reds. An oxidizing process due to a ferment. Haemoglobin, either → methaemoglobin (wont yield O as readily as oxyhaem.), or → haemoglobin

by considerable diuresis from a similar action in the kidney. In the great majority of cases no further effects are observed.

In some individuals, however, symptoms arise from the chlorate action quite apart from those mentioned above, which may be induced by any diffusible salt. These chlorate symptoms may be divided into those of acute and of subacute poisoning, the first arising generally from the administration of a single large dose, the second from smaller quantities taken repeatedly. In **Acute Chlorate Poisoning**, the first symptom is often prolonged and violent vomiting, with pain in the stomach region; diarrhœa and a dark cyanotic color of the skin and mucous membranes follow, the respiration is at first dyspnœic and then weak, the pulse quick and feeble, sometimes irregular. The patient complains of headache, giddiness and muscular weakness, is restless, and eventually becomes comatose before death.

In **Subacute Poisoning**, vomiting and diarrhœa are also observed, and the vomited matter often contains large quantities of bile, less often blood. There may be complete anuria for some time, or the urine is scanty and at first dark colored, then deep reddish-brown; it contains hæmoglobin, methæmoglobin, and hæmatin in solution. On standing, it deposits casts of brown amorphous particles, which arise from the destruction of the red cells of the blood, and chlorates are contained in it in considerable quantity. The methæmoglobin may disappear from the urine after one or two days, but the casts remain longer. The skin is often icteric in color, and in some cases erythematous eruptions have been observed. Headache, muscular weakness and abdominal pain are complained of, and uræmic symptoms may arise—delirium and convulsions, or confusion and coma. Death has followed from these last as late as a week after the first symptoms of poisoning were observed, but in several cases complete recovery has followed even the gravest symptoms.

Action.—The cause of the symptoms in acute and subacute chlorate poisoning is, apart from the salt-action, a specific effect which the chlorates have on the **Red Blood Cells** and particularly on the **Hæmoglobin.** This is seen especially well when blood is added to a chlorate solution outside the body, for in course of a short time the blood assumes a dark chocolate brown color, and spectroscopic examination reveals the absorption bands of methæmoglobin and often of hæmatin. After a time the red blood cells tend to break up, and the methæmoglobin is freed in the serum. If large quantities of chlorates be added, the blood becomes quite black in color, and assumes a gelatinous consistency. This action on the blood is generally ascribed to their oxidizing properties, for other oxidizing agents have the same effects; the exposure of hæmoglobin to such bodies leads to the formation of methæmoglobin, while the red blood cells are destroyed and the hæmoglobin is liberated in the plasma; the two processes seem to proceed independently of each other, for some oxidizing agents induce marked hæmolysis with little methæmoglobin, while in others the latter feature is the predominating one. There is however some difficulty in

Result – asphyxia of tissue. If not death may have change back to haemoglobin, or corpuscles containing it may be broken up & metah. + haem + debris excreted in urine, or deposited in spleen liver &c. Bile increased – absorption = jaundice. It may block tubules = uremia poisoning.

explaining the chlorate action by oxidation, for these salts are very stable and have practically no oxidizing action at body temperature. It is probable, however, that in the blood and tissues they come in contact with a ferment which is capable of freeing the oxygen.

When this transformation of the hæmoglobin takes place in the vessels, the blood is unable to supply the tissues with oxygen, because in methæmoglobin the oxygen is attached much more firmly than in oxyhæmoglobin, and the tissues are incapable of availing themselves of it. If much of the hæmoglobin is thus rendered useless, asphyxia results, and this is unquestionably the chief cause of the symptoms and of the fatal issue in the most acute form of intoxication. If a smaller amount of methæmoglobin is formed, it disappears gradually, either by being slowly reformed to hæmoglobin, or by the corpuscles containing it being withdrawn from the circulation and broken up. When a considerable amount of hæmoglobin is transformed, but sufficient remains to continue the respiration of the tissues, the subacute form of poisoning results. The blood cells break up and the hæmoglobin, methæmoglobin and the débris of the corpuscles thus freed in the plasma are in part excreted by the urine, in part deposited in the spleen, liver, and bone marrow. As in other conditions of excessive destruction of the red blood cells, the bile pigment is increased in amount, and its absorption from the bile capillaries induces jaundice. The excretion of the products of the destruction of the red blood corpuscles in the urine leads to the renal tubules becoming stopped up with brown granular masses, which are in part forced downwards and appear in the urine as casts, but which may lead to an almost complete suppression of urine and to symptoms of uræmic poisoning. In those cases in which death follows several days after the first symptoms, it seems due not to the direct action of the poison, but to the renal changes. Often no actual nephritis is present, but in some cases the epithelial cells seem to be inflamed, probably as a secondary result of the plugging of the tubules. The deposition of the débris in the liver and spleen often causes enlargement of these organs. In these subacute cases of poisoning, then, death is not due directly to the methæmoglobin formation, but to the breaking down of the red cells.

The post-mortem appearances in chlorate poisoning vary with the form. In acute poisoning the characteristic color of the blood, and the methæmoglobin absorption band in the spectrum are often the only distinct appearances. In less acute cases, the débris of the red corpuscles is found in the liver, spleen, bone-marrow and renal tubules, while no methæmoglobin may be detected. Some of the red blood corpuscles are found misshapen, however, others are colorless (shadows), and in some the pigment is formed in masses, instead of being generally diffused. Some swelling and ecchymoses of the gastric and intestinal mucous membrane have been observed.

The hæmoglobin of most animals seems equally easily transformed to methæmoglobin by chlorates when it is dissolved in water, but the

Nervous sy. due to blood changes & uremia. Little reduced in blood & tissues as 90% recovered in urine. Bromates & iodates more poisonous than chlorates - Perchlorates = convulsions & increase of reflex excitability etc

blood corpuscles of the rabbit and guinea-pig resist their action much more than do those of the dog and of man. Rabbits therefore very rarely show any symptoms of true chlorate action, and die of the potassium or of the salt-action, while dogs and cats exhibit symptoms very like those seen in man. The cause of this immunity of the rabbit's corpuscles is unknown, but may perhaps be explained by their being impermeable by the chlorate salts. It has been found that when the rabbit's blood is concentrated, or when bile is present in quantity in it, the chlorate action may be elicited much more readily than in normal animals.

The nervous symptoms in chlorate poisoning are manifestly due to the blood changes and the uræmia for the most part, though there is reason to believe that under some conditions the brain is also directly affected. The heart is said to be first slowed and then accelerated by the intravenous injection of sodium chlorate. The vomiting does not seem to be due to local action only, for it is seen in animals in which the salt is injected subcutaneously.

Very little chlorate is reduced in the blood and tissues, for 90–96 per cent. of the amount administered has been recovered from the urine. Small quantities appear also in the saliva and in other secretions, such as the perspiration, milk, tears, and nasal mucus, and some has been found to pass from the mother to the fœtus in utero.

The chlorates are hardly more antiseptic than other indifferent salts.

The **Bromates** and **Iodates** have been much more seldom the subject of investigation than the chlorates, and are not used in therapeutics. The iodates are more poisonous than the bromates and these again than the chlorates; the iodates destroy the red cells more rapidly but form less methæmoglobin than the chlorates in test-tube experiments. Iodates induce fatty degeneration of the liver and congestion and extravasation in the alimentary tract. Some iodide is formed from them in the body.

The action of the **Perchlorates** has been examined by Kerry and Rost. In the frog the perchlorate of sodium ($NaClO_4$) induces fibrillary twitching and clonic contractions of the muscles; the contraction of the muscle is prolonged in the same way as by veratrine, and rigor eventually follows as in caffeine poisoning. The reflex excitability is increased and the heart is slow and irregular. The effects of the perchlorate on mammals differ considerably in different species; in the rat, mouse and guinea-pig the reflex excitability is enormously increased and tetanic convulsions may arise from this action; in the cat a certain stiffness, muscular paresis and tremor can be made out after the injection of large quantities of perchlorate, but these animals as well as the rabbit and dog are not killed by even very large quantities.

PREPARATIONS.

0.3–1g ✓ POTASSII CHLORAS (U. S. P., B. P.) ($KClO_3$), 0.3–1 G. (5–15 grs.).

TROCHISCI POTASSII CHLORATIS (U. S. P.) contain 0.15 G. (2½ grs.) chlorate of potassium in each lozenge.

TROCHISCUS POTASSII CHLORATIS (B. P.) contains 3 grs. in each.

Sodii Chloras (U. S. P.) ($NaClO_3$), 0.25 G. (4 grs.).

The chlorates are colorless prismatic crystals with a saline taste, and are given in solution or in lozenges when used internally. The dry salts form

Salts + organic or other reducing substances + heat or rubbing = explosion. Use - irritation of throat & mouth & ulcers - as a wash. Prophylactic against stomatitis. In catarrh of throat. 2-4% sol. Action probably salt action. Does not give up O to blood. Nephritis cases esp susceptible to poisoning. Emesis diuresis make blood alkaline.

explosive mixtures with organic or other reducing substances, and such mixtures are therefore to be kept cool, and ought not to be ground together, as heat and pressure are liable to cause explosions.

Therapeutic Uses.—The chlorate of potassium is used chiefly as a mouth wash and gargle in irritable conditions of the mouth and throat, such as aphthæ, and in the tenderness and ulceration of the gums and mouth induced by the prolonged use of mercury. It may also be given as a prophylactic to prevent stomatitis when mercury is being prescribed, but it does not prevent the salivation. In catarrh of the throat the chlorate of potassium is often used with apparently good effects. It has been strongly advised in diphtheria, but is of only questionable value here.

The chlorate of potassium is more frequently prescribed than the sodium salt, but the latter seems equally efficient. The chlorates are used in 2–4 per cent. solution, or the official lozenge may be prescribed. In children a somewhat stronger solution with syrup or honey may be used to brush out the mouth, but care should be taken that none is swallowed. The local action of the chlorates has not been explained, and it may be due to the salt-action in part, though not wholly. It has been suggested that they are oxidizing disinfectants, but there is no reason to suppose that they are changed here any more than in the tissues in general. It is not impossible that equally satisfactory results might be obtained by the use of the chlorides or nitrates. Chlorate of potassium has been given internally in cases of diphtheria and in some diseases of the mouth, but it does not seem to have any therapeutic value unless when applied locally. Some benefit may arise from its contact with the mouth and throat in the process of swallowing and from its excretion in the saliva. In addition the internal administration of the chlorate is liable to induce dangerous poisoning. It is unnecessary to discuss the earlier uses of the chlorate, which were based on the theory that it gave up its oxygen to the blood, for both theory and practice have been shown to be erroneous.

Poisoning.—The fatal dose of chlorate varies extremely, as little as 1 G. (15 grs.) having proved fatal in a child, while 40–50 G. (10–12 drs.) have been swallowed by adults without marked symptoms. There is no question that the red blood cells are often peculiarly susceptible to the action of the chlorates; poisoning is especially common in nephritis. In cases of poisoning the stomach should be evacuated, if any of the salt is believed to remain in it, but the symptoms often appear only 2–3 hours or longer after the drug has been taken. General treatment with central nervous stimulants, ice for the vomiting, etc., may be carried out. The formation of methæmoglobin is less liable to occur when the blood is more alkaline than usual, and this has led to the administration of the alkaline carbonates in these cases. After the acute symptoms pass off diuretics are often advised, and large quantities of fluid are given in order to flush out the kid-

[illegible]
w. Ad. . then little danger of poisoning!

neys and prevent as far as possible the tubules from being stopped up by detritus.

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XI. NITRATES.

The nitrates are generally supposed to have little action except that of salts in general, and have been comparatively seldom the subject of pharmacological examination. In small doses they induce changes very similar to those seen after the chlorides, but there is little doubt that in addition to the salt-action, a distinct nitrate-ion effect exists, and is manifested chiefly in irritation of the mucous membranes which are exposed to it.

Symptoms.—The nitrates have a cool, saline taste, and in small doses induce no symptoms save an augmented flow of urine. Large quantities, however, cause gastro-intestinal irritation, giving rise to pain in the stomach region, nausea, vomiting and sometimes diarrhœa, and blood may be present in the vomited matter and in the stools. The urine is often abundant, but may be scanty or entirely suppressed. These symptoms may be followed by great muscular weakness, apathy, collapse and eventually coma and death.

At the autopsy the stomach and intestines are found red and congested, and very often contain blood extravasations. The kidney is said to have presented the symptoms of acute nephritis and hæmorrhages in some cases of poisoning.

When dilute solutions of the nitrates are used, much less irritation is induced, and in fact large quantities may be taken thus without causing any symptoms whatever except diuresis.

Action.—Very similar effects may be induced by large quantities of common salt, or of potassium chloride, and it is therefore often stated that the nitrates act in the same way as the chlorides. But this is not entirely correct, for while there is no question that the salt-action explains much of the effect of the nitrates, these salts have a specific irritant action. Thus very much smaller quantities of the nitrates than of the chlorides are sufficient to induce serious irritation, and solutions of the nitrates isotonic with the blood induce irritation and congestion in the intestine and are slowly absorbed. This irritant effect of the nitrates has been explained by Binz and Barth as the

Normally some in urine. That in urine tho increased ½ disappears. Some nitrite formed, this → NH_3 → N lungs.
KNO_3 – Saltpetre 0.3–2 G – in dil sol. Only in diuretic mixtures with care in g.i. irritation.

Burning on paper to relieve spasm of bronchial muscles in asthma, or in cigars.

result of the reduction of the nitrates to nitrites in the alimentary canal and tissues, but no symptoms of nitrite action seem to have been observed in cases of poisoning with nitrates. Haldane has recently shown that nitrite is formed from the nitrate used in the preservation of meat by salting, and that some nitrous-oxide hæmoglobin is formed and gives a bright red color to the meat. The presence of this pigment may perhaps explain the red color of the intestine in some cases of poisoning in which extravasations of blood are not marked.

The nitrates have long been used as diuretics, more especially the nitrate of potassium. The diuresis is generally attributed to the salt-action, but there may be in addition a true stimulation of the kidney similar to that observed under the action of many other drugs which are irritant to the bowel. The nitrate of potassium is generally considered a better diuretic than the sodium salt.

The Fate of the Nitrates in the Body is still unknown, and in fact seems to vary in different animals and under different conditions. In man and in most animals, some nitrate is present in the urine normally, apparently derived from vegetable food, although it may in some cases be one of the final products of the protein metabolism. Large doses of nitrates given by the mouth lead to some increase in the nitrate in the urine, although more than half of that ingested disappears entirely in the tissues. Nitrite has also been found in the urine after large quantities of nitrates in animals and the nitrite reaction is obtained from a number of organs. When smaller amounts of nitrate are swallowed (1–3 G. in man), no increase in the nitrate of the urine is observed, the whole of that ingested being changed to some other form in the tissues. It is surmised that the nitrate is reduced first to the nitrite, and then to ammonia, or that it is eventually excreted by the lungs as free nitrogen. Some of the nitrate seems to be excreted in the saliva and perspiration, possibly unchanged, although it is rapidly reduced to nitrite in these secretions, and may in fact be changed to this form in the secretory cells.

The action of the nitrates on the individual organs is practically entirely unknown. They have a weak hæmolytic effect in the blood.

Richet has found solutions of the nitrate of sodium less harmful to fish living in it than those of any other salt except the chloride.

PREPARATIONS.

Potassii Nitras (U. S. P., B. P.), Nitre, Saltpetre (KNO_3), 0.3–2 G. (5–30 grs.). 0.3–2 G

Sodii Nitras (U. S. P.), Chili Saltpetre ($NaNO_3$), 0.3–2 G. (5–30 grs.).

The nitrates form colorless crystals with a cool, saline taste. They are very soluble in water and are prescribed in dilute solution.

Therapeutic Uses.—The nitrates are seldom used now except as ingredients of diuretic mixtures; *e. g.,* along with digitalis. The nitrate of potassium was formerly employed largely in fevers and in various disorders of the metabolism, such as rheumatism or gout, but in none of these has it been found useful. The nitrates are to be given with care when there is any irritation of the stomach and intestine. Authorities differ as to whether they may be prescribed in irritation of the kidney, but in every case they ought to be well diluted.

Paper impregnated with saltpetre is used in asthma by burning it in the sick room, when the pyridine and nitrites relieve the spasms by relaxing the bronchial muscles. Saltpetre may be used in cigars or cigarettes for the same purpose, and the tobacco may contain also the leaves of belladonna or some of its allies, as these have a special action on the bronchial muscle.

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XII. SULPHITES.

The sulphites, an unimportant group of bodies from a therapeutic point of view, have been shown to have a more poisonous action than many better known salts. They possess fairly strong antiseptic properties, because they withdraw oxygen from organic matter in order to oxidize themselves to sulphates. Injected into frogs, sulphite of soda causes great muscular weakness and depression, and eventually paralysis of the central nervous system, beginning in the brain and descending to the spinal cord. Later, the heart becomes weak and ceases in diastole, and the peripheral nerve terminations and the muscles are paralyzed. In mammals the action is exerted chiefly on the medulla oblongata and the heart. In the dog and cat subcutaneous injection causes nausea, vomiting, restlessness and dyspnœa and great muscular weakness, ending in arrest of the respiration, and a little later of the heart. In the rabbit the symptoms consist of dyspnœa, muscular weakness without loss of spontaneous movement, and finally death from failure of the respiration and the heart.

Much larger quantities are required to poison animals when given by the mouth than when injected subcutaneously, probably because the salt is slowly absorbed from the alimentary tract, and also because some of it is changed to the harmless sulphate before it reaches the blood. Some irritation of the stomach is caused from the sulphurous acid being freed by the gastric juice, and this induces vomiting in the dog.

Intravenous injection shows that the chief seat of action of the sulphites is the medulla oblongata, in which they depress the respiratory and vasomotor centres. The heart is acted on directly apparently, for the pulse is slow, and the muscular walls of the vessels are also weakened. Kionka states that sulphites destroy the red cells of the blood, and that infarcts are formed from their remains in the vessels and lead to hæmorrhages in many organs.

If large quantities be absorbed rapidly, they prove immediately fatal, but if the respiration be kept up for a short time, recovery may follow, because the poisonous sulphite is changed to the harmless sulphate and excreted. Almost all of the sulphite absorbed into the blood is oxidized to the sulphate, a mere trace being excreted in the urine unchanged. The thiosulphate is apparently oxidized with greater difficulty, for Walko found 30–50 per cent. eliminated by the kidneys unaltered.

Large doses of sulphites have been taken by man without symptoms of poisoning being induced. Even 30–40 gms. are said to have been swallowed, but in most preparations of sulphite a large proportion of sulphate is present, and it is impossible to state how much sulphite was really contained in these doses. Symptoms of gastric and intestinal irritation have been induced by comparatively small quantities, and Kionka found that even smaller doses of sulphite administered daily to animals caused hæmorrhages in different organs, and accordingly condemns the use of sulphites to preserve meat, wines and vegetables; in addition they seem to have little effect in preserving meat from putrefaction, though they improve its appearance.

Sodii Sulphis (U. S. P., B. P.) ($Na_2SO_3 + 7H_2O$), a soluble salt which oxidizes to the sulphate in the air, is feebly alkaline and has a cool, saline taste. 0.3–2 G. (5–30 grs.).

Sodii Bisulphis (U. S. P.) ($NaHSO_3$) has a disagreeable odor of sulphurous acid, an unpleasant taste and an acid reaction. 0.5 G. (8 grs.).

Sodii Thiosulphas (U. S. P.) ($Na_2S_2O_3 + 5H_2O$) is very soluble, has a cool, saline taste and is neutral in reaction. 1 G. (15 grs.).

Solutions of these salts have been used to a limited extent as antiseptic mouth-washes in aphthæ, and have been prescribed in some forms of fermentation in the stomach. They were formerly reputed to be of benefit in cases of pyæmia from their supposed action as antiseptics in the blood, but have never been shown to be of any real value.

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XIII. HYPOPHOSPHITES.

The hypophosphites have been used in therapeutics in the belief that they had some special influence on nutrition. They were formerly supposed to be oxidized in the tissues to the phosphates, but this has been shown to be incorrect, as practically the whole of the hypophosphite administered can be recovered unchanged from the urine. No entirely satisfactory work on the effects of these salts on the nutrition has been done, but there is no ground to suppose that they have any further action than the other indifferent salts, such as the chlorides. The chief effect of the hypophosphite of iron is undoubtedly due to the metallic ion.

PREPARATIONS.

Sodii Hypophosphis ($NaOPH_2O$) (U. S. P., B. P.), 0.2–1 G. (3–15 grs.).

Potassii Hypophosphis ($KOPH_2O$) (U. S. P.), 0.5 G. (8 grs.).

Calcii Hypophosphis ($Ca(OPH_2O)_2$) (U. S. P., B. P.), 0.2–0.6 G. (3–10 grs.).

Ferri Hypophosphis ($Fe_2(OPH_2O)_6$) (U. S. P.), 0.2 G. (3 grs.).

Acidum Hypophosphorosum dilutum (U. S. P.), 0.5 c.c. (8 mins.).

Syrupus Hypophosphitum (U. S. P.) contains the hypophosphites of calcium, potassium, sodium, free hypophosphorous acid, spirit of lemon and sugar, 8 c.c. (2 fl. drs.).

Syrupus Hypophosphitum Compositus (U. S. P.) contains, in addition to the constituents of the above, iron, manganese, quinine, strychnine and sodium citrate. 8 c.c. (2 fl. drs.).

Therapeutic Uses.—The hypophosphites are used in weakness and cachexia

Halogens leave ali canal easily. Salts of metals difficulty.
Na + K sulphates. phosphates, citrates & tartrates. alk. earth ions & these acid radicles penetrate with difficulty.

✓

and especially in commencing phthisis and anæmia. The syrup with or without iron is the form in which they are invariably prescribed. There is a popular belief that they improve digestion and nutrition, but most reliable investigators deny that they have any other influence than the better known and cheaper salts of iron, calcium, etc.

XIV. SALINE CATHARTICS.

Dilute solutions of such salts as the chlorides, iodides and bromides of the alkalies are absorbed rapidly from the alimentary canal, but some of the other salts of these metals apparently permeate the epithelium with greater difficulty, and their solutions therefore remain unabsorbed for a longer time in the intestine. Little is known of the effects of these salts in the tissues, but their action in the intestine has led to their therapeutic use, and they may therefore be classed together as the saline cathartics, in order to distinguish them from the rapidly absorbed salts, such as the chlorides, or bromides. The chief salts of sodium and potassium which have this intestinal action are the sulphates, phosphates, tartrates and citrates; less known ones are the malates and ferrocyanides.

It is manifest that the peculiar effect of these salts is due to the acid constituent, or anion, and not to the base or kation, for the latter may be present in readily absorbable salts, such as chlorides. All combinations in which the sulphate, phosphate, etc., ion is found, therefore, are less easily absorbed than the corresponding ones with bromide or chloride ions. But these cathartic anions are only weakly active, and no pronounced difference can be observed in the action of chlorides and sulphates, unless the salt can be given in large quantities, as is possible in the case of the salts of the alkalies. The effects of the sulphate and hydrochlorate of morphine, for example, may be taken as identical, because the anion is present in so small amount as to be practically inert.

The chloride ion is rapidly absorbed, as is seen in the case of sodium chloride. Yet when the chloride of magnesium is administered, it disappears only very slowly from the bowel. It would seem, therefore, that the magnesium is also more slowly absorbed than the sodium and potassium ions, and that cathartic action can be obtained from either basic ions (kations) or from acid ions (anions). When both ions of a salt are slowly absorbed, the cathartic action is, of course, more powerful than when one is rapidly absorbed. Thus, magnesium sulphate is a more powerful purgative than either magnesium chloride or sodium sulphate, because in the first both ions are difficult of absorption, while in the others only one is cathartic. It seems probable that all the alkaline earth ions resemble magnesium in permeating the epithelium with difficulty.

The chief saline cathartics used in therapeutics are the *sulphate of sodium* (Glauber's salt), the *sulphate of magnesium* (Epsom salt), the *double tartrate of sodium and potassium* (Rochelle salt) and the *citrates of potassium and magnesium.* In addition the *oxide* and *car-*

Bitter unpleasant. Nausea as any other salt (cm). Dil = watery stools. Less pain. griping & irritation than vegetable purges. Non absorption, increased fluid. & distension = peristalsis

bonate of magnesium have some purgative action from being formed into soluble salts in the stomach and intestine. But besides these, many other salts are slowly absorbed and might therefore be used for this purpose. Thus the sulphates, citrates, or tartrates, of any of the alkalies or of the non-poisonous alkaloids might be used for this purpose, provided they are soluble, and any of the magnesium salts might be used in the same way.

Symptoms.—The external application of solutions of the saline cathartics has the same effect as that of any other indifferent salt, such as sodium chloride.

Most of the cathartics have a harsh, bitter, unpleasant taste, and when taken in concentrated solution, may induce some nausea, partly from the taste, and partly from their effect on the stomach, which is the same as that of solutions of sodium chloride of similar concentration. Dilute solutions, however, provoke no such symptoms, but after one or two hours induce a profuse watery evacuation of the bowels. This is sometimes preceded by some pain and griping, but these are not nearly so frequent or so severe as after the vegetable purgatives. Not infrequently the urine is increased in amount afterwards, or it may be found to have an unusually high percentage of salts. If a moderate quantity of a dilute solution be given, only one evacuation follows, but large doses of concentrated solutions induce repeated stools, which at first contain some fæcal matter, but later consist mainly of bile-stained mucous fluid.

Action: Intestine.—The explanation of the action of the saline cathartics has been much debated, and the details have not even yet been entirely settled. One point is, however, perfectly certain—the saline cathartics differ from the vegetable purgatives in not inducing irritation of the intestine, unless when they are given in very large quantities. The characteristic effect is not irritation, but retarded absorption. If a solution of sodium chloride isotonic with the blood serum be administered by the mouth to a dog with a cæcal fistula, little or none of it reaches the wound, as it is all absorbed in the stomach and small intestine. If, on the other hand, an equal amount of an isotonic solution of sodium sulphate be administered in the same way, the most of the solution escapes by the fistula, only some 10–20 per cent. having been absorbed by the stomach and small intestine. In a normal dog or in the human subject, a much larger amount of fluid therefore reaches the large intestine if sodium sulphate be dissolved in it than if sodium chloride be used instead. The contents of the large intestine are consequently more fluid than usual, and are passed down more easily towards the rectum. At the same time the weight and distention of the bowel induces increased peristalsis and the whole is evacuated. This increased peristalsis is due, however, not to any irritant action such as has been found to be induced by rhubarb or croton oil, but to the large amount of fluid contents.

If a weaker solution of sodium sulphate is administered, the only

Isotonic or hypo — of saline cathartics = non absorption — causes fluid watery stools. distension + increased peristalsis — not irritation. Hypertonic salts = hydragogue — only slight absorption. Takes up oedema and dropsy thru blood.

difference is that more of the fluid is absorbed and less reaches the large intestine; but however weak the solution, more of it reaches the large intestine than if a correspondingly weak solution of common salt had been given.

If a hypertonic solution be administered, the effect is somewhat different. The salt is still unabsorbed, but it draws fluid from the blood into the bowel from its having higher osmotic pressure than the blood. A similar draining of the body fluids occurs when concentrated solutions of common salt reach the bowel, but the cathartic salts are much more powerful, because they do not pass out of the bowel into the blood so easily. Instead of an exchange of salt and fluid being carried on by the blood and intestinal contents, the blood gives up its fluid without any sufficient compensation in salt. Eventually the intestinal fluid becomes isotonic, and then some absorption of both salt and fluid occurs; in fact, some salt has been absorbed all along, as the epithelium is not absolutely impermeable to the cathartics. But much less of the sulphate is absorbed than of the chloride given in equal concentration, and as a general rule a strong solution causes such an accumulation of fluid that the bowel becomes distended and evacuates its contents. If, however, from any cause this fails to occur, a gradual absorption follows and the whole salt and fluid in the bowel is absorbed. These salts may fail to purge, for example, when the blood and tissues contain very little fluid, as in animals which have been deprived of water for several days previously. In this case the osmotic pressure in the bowel is unable to draw fluid from the concentrated blood, which on the other hand has a higher attraction for the fluid in the bowel than usual. But where large quantities of fluid are present in the tissues, as in œdema and dropsy, the saline cathartics drain them through the blood into the bowel, and very profuse evacuation occurs, with the disappearance of the exudate.

There is still some doubt as to why the saline cathartics are so slowly absorbed from the intestines, but the most widely accepted view is that they fail to penetrate into the cell, exactly as the salts of the metals fail to penetrate the red blood cells, that there is a distinct affinity between the bowel epithelium and the chloride of sodium, but only a much weaker one between it and the cathartics, which therefore fail to permeate it. The acceptance of this view does not involve the rejection of the belief that the cell is actively engaged in absorption, for it is difficult to explain how a solution after penetrating the superficial layers of the epithelium is passed on from them to the blood except by assuming that the cell exercises some propelling force, which may be exerted only during its life.

The further question arises, why the intestinal epithelium should be permeable by certain salts such as the chloride of sodium and impermeable by others (sulphate of sodium). In this relation it has been found by Hofmeister and Pauli that the purgative salts have a greater tendency to precipitate proteins and have less tendency to permeate into unorganized colloids than most of the non-purgative

Hyper - non-absorption by blood of digested fluids - con. of blood. thirst little urine. If purgation not soon, salts absorbed slowly, & then diuretic action (not practical use - a little resorbed)

salts. In numerous other instances the sulphates, tartrates, and other cathartic anions have proved slower in permeating into living cells than the chlorides and bromides, and their effects on the blood cells, muscle, nerve, and some other tissues show marked deviations from those of the halogen salts. It is impossible to determine at present how far the action of these anions is explained by their slow permeation and how far a more specific action is involved, but there can be no question that the former factor is the predominant one in many of these reactions. Another curious relation between the purgative anions is that their calcium salts are all very much less soluble than those of the salts which penetrate the epithelium, but whether this is merely a coincidence or not is uncertain. Most of the cathartic anions are bivalent or trivalent, but this is not true for all of them, for the higher members of the acetate series are absorbed with the greatest difficulty by the intestine.

The saline cathartics induce certain changes in the **Blood** indirectly through their action on the intestine. They prevent the absorption of the fluid of the food, or, if in sufficient concentration, actually draw fluid from the blood and tissues into the bowel, and under both conditions the blood becomes more concentrated than usual; in the first case because it is not reinforced by the usual amount of fluid from the food, in the second because it actually loses fluid into the intestine. This concentration of the blood leads to a sensation of thirst, and to a lessened excretion of fluid by the kidneys and other glands.

A certain amount of salt and of fluid is absorbed from the intestine, unless purgation follows very rapidly, and this salt acts in the blood and tissues in the same way as the salts which do not act as cathartics. When very dilute solutions of these salts are given, therefore, the effect is similar to that of ordinary salt, except that the hydræmia and the diuresis do not follow so soon, because the absorption is somewhat slower. Stronger cathartic solutions at first cause a concentration of the blood and lessened urine, but afterwards the excess of salt in the blood may cause diuresis. The greater the purgative action, the less the diuretic, because more fluid and more of the cathartics are thrown out in the stools. If no purgation follows for any reason, as when the blood has been concentrated by long abstinence from water, the whole of the salt eventually passes into the blood and is excreted by the kidney, and may cause very considerable diuresis and a still further concentration of the blood. The sulphates are absorbed by the epithelium of the renal tubules with much greater difficulty than chloride, and thus offer osmotic resistance to the absorption of the fluid in the tubules; sulphates absorbed into the blood therefore induce a more diffuse diuresis than an equal amount of chloride, but less of the former reaches the blood generally, so that the chlorides are better practical diuretics.

From the above it can be at once inferred that a saline cathartic injected intravenously causes no purgation, for instead of preventing the passage of fluid from the bowel into the blood, it rather encourages

Hypo = no purge. Fat cure – prevents proteins & fat from reaching blood + depletes tissues of fluid.

its absorption by increasing the osmotic pressure of the blood. And similarly the hypodermic injection of these salts is not followed by purging. A certain amount of discussion has been carried on in the last few years on this point, but the result has been to confirm this view and to indicate that experiments which seemed to oppose it were erroneously performed.

The statement is sometimes made that the saline cathartics act as cholagogues, *i. e.,* increase the secretion of bile, but this has not been confirmed by more careful observations.

The **Temperature** is often somewhat reduced by the action of the saline cathartics, but seldom more than one half degree.

The habitual use of saline cathartics is often efficient in **Reducing the Weight** in obesity, and many of the natural mineral waters have a considerable reputation in the treatment of such cases. This appears to be due in part to less proteins and fats being absorbed from the intestine, in part to the fluids of the body being decreased. There seems no reason to suppose that any marked change in the nitrogenous metabolism is induced by the cathartics, for the nitrogen in the urine is often practically unaltered in amount.

When purgation follows the administration of a saline cathartic, the most of the salt escapes in the fæces, never having been absorbed at all. When the salt fails to purge, however, and is absorbed, it undergoes the usual exchanges in the tissues and is excreted by the urine. There is no reason to suppose that any of it appears again in the stomach or intestine.

The **Sulphates** seem to pass through the tissues without injuring them, and but little effect is observed from injecting considerable quantities into the blood. When the sulphate ion is combined with a poisonous base, such as potassium or magnesium, the injection is of course followed by characteristic symptoms; but the anion seems to be comparatively harmless, and when the potassium or magnesium salt is taken by the mouth it also is quite devoid of general action.

The **Phosphates** are also very inactive after absorption. Gamgee found the orthophosphate quite harmless, while the metaphosphates and pyrophosphates are poisonous, more especially the last, when injected subcutaneously or intravenously. Phosphates absorbed in man and in the carnivora are excreted by the kidney and increase the acidity of the urine; in the herbivora they are excreted exclusively by the bowel wall.

The **Citrates** are rapidly oxidized in the tissues to carbonates, and only traces of the unchanged salt escape in the urine. The urine may thus be rendered alkaline by the administration of the citrates, especially in small quantities which are insufficient to induce purgation (see hydrates and carbonates of the alkalies, page 547). The **Tartrates** are more slowly oxidised, and a considerable quantity is excreted in the urine unchanged. Injected into the blood directly, the citrates and tartrates seem to act as heart poisons, but very little is known in regard to this point.

The **Magnesium Salts** have recently been shown by Meltzer to have a very powerful action when injected hypodermically or intravenously. The most characteristic effect is complete anæsthesia, resembling that induced by the chloroform group, and ending in fatal cases in paralysis of the respiratory centre. This arises from direct affection of the central nervous system, and immediate recovery follows the injection of a calcium salt, which opposes the

Mg. salts anaesthetic. IV poisonous - neutralized by Ca [illegible]
By mouth eliminated rapidly so no poisonous effect.

magnesium action in the same way as it does that of pure sodium (see Calcium). Applied to a nerve trunk, magnesium salts in 25 per cent. solution act in the same way as cocaine, paralyzing first the afferent and later the efferent fibres, and injected into the intradural space they cause complete anæsthesia of the lower part of the body like cocaine; magnesium sulphate has, in fact, been substituted for cocaine occasionally for surgical operations and in the treatment of tetanus. The anæsthesia lasts very much longer and this renders it unsuitable for surgical work, but several cases of tetanus treated by subdural injection of magnesium sulphate have recovered. (Dose, about 0.02 G. per kg. in man.) Magnesium has comparatively little effect on the heart, tending to lessen the excitability of the vagus, and this effect may also be abolished by lime salts. It reduces the irritability of the intestine when injected intravenously and arrests the peristalsis aroused by physostigmine or barium. It also appears to have some effect on the myoneural receptors in muscle, for it arrests the twitchings induced by physostigmine and in large doses interrupts the path from nerve to muscle in the same way as curara. When injected intravenously magnesium proves to be considerably more poisonous than potassium, but, unlike the latter, kills by paralyzing the respiration. None of these effects are elicited when magnesium salts are given by the mouth, as that absorbed is excreted rapidly and there is never enough accumulated in the blood to have any action. Magnesium is excreted by the kidney and traces may appear in the secretions from other organs. It is eliminated rapidly, the whole appearing in the urine within 48 hours, and this excretion of magnesium is attended by an increase in the calcium of the urine, while that of the fæces may diminish.

The oxide and carbonate of magnesium differ from the other saline cathartics in being very insoluble and in possessing an alkaline reaction. Part of that ingested is formed into magnesium chloride in the stomach, however, and the carbonic acid present in the intestine may dissolve part by forming the bicarbonate. Their alkalinity serves to remedy any excessive acidity of the stomach or intestine, while at the same time they are mildly cathartic. The prolonged use of large quantities of magnesia has in some cases led to the formation of large concretions in the bowel, resulting in obstruction.

PREPARATIONS.

SODII SULPHAS (U. S. P., B. P.), Glauber's salt (Na_2SO_4, $10H_2O$), soluble in about 3 parts of cold water, 2–30 G. (30 grs.–1 oz.). 2-30 g 1:3 water

MAGNESII SULPHAS (U. S. P., B. P.), Epsom salts ($MgSO_4$, $7H_2O$), soluble in 1½ parts of cold water, 2–30 G. (30 grs.–1 oz.). 2-30 g 1:1½ wa

Potassii Sulphas (U. S. P., B. P.), 1–4 G. (15–60 grs.).

These are crystalline salts with a harsh, bitter taste.

SODII PHOSPHAS (U. S. P., B. P.) ($Na_2HPO_4 + 12H_2O$), soluble in about 6 parts of cold water, 1–30 G. (15 grs.–1 oz.). 1-30 1:6

Sodii Pyrophosphas (U. S. P.) ($Na_4P_2O_7 + 10H_2O$), 2 G. (30 grs.).

These are crystalline salts with a cool, saline taste.

Liquor Sodii Phosphatis Compositus (U. S. P.) contains sodium nitrate and citric acid. Dose, 8 c.c. (2 fl. drs.).

Sodii Phosphas Exsiccatus (U. S. P.), dried sodium phosphate, 1 G. (15 grs.).

Potassii Bitartras (U. S. P.), *Potassii Tartras Acidus* (B. P.), cream of tartar ($KHC_4H_4O_6$), 1–4 G. (15–60 grs.).

POTASSII ET SODII TARTRAS (U. S. P.), SODA TARTARATA (B. P.), Rochelle salt ($KNaC_4H_4O_6 + 4H_2O$), soluble in 1.4 parts of cold water, 8–16 G. (120–240 grs.). 8-16 g 1:1.4

Na + Mg SO_4, Rochelles + Na_2HPO_4 (5–10% maximum) in water or milk
Effervescent salts in sol in tumbler of water

Potassii Citras (U. S. P., B. P.) ($C_3H_4OH(COOK)_3$), 1–3 G. (15–45 grs.).

Lithii Citras (U. S. P., B. P.) ($C_3H_4OH(COOLi)_3 4H_2O$), 0.3–0.6 G. (5–10 grs.).

Sodii Citras (U. S. P.) ($2C_3H_4OH(COONa)_3 + 11H_2O$), 1 G. (15 grs.).

These form salts with a cool, saline or, in the case of the bitartrate, acidulous taste. They are all very soluble in water, except the bitartrate. The citrates are not purgative in the dose given.

Magnesii Oxidum (U. S. P.), Magnesia Levis (B. P.), light or calcined magnesia (MgO).

Magnesia Ponderosa (B. P.), Magnesii Oxidum Ponderosum (U. S. P.), heavy magnesia (MgO).

Magnesii Carbonas (U. S. P.) ($(MgCO_3)_4Mg(OH)_2 + 5H_2O$).

✓Magnesii Carbonas Levis (B. P.)
✓Magnesii Carbonas Ponderosa (B. P.) } ($3(MgCO_3), Mg(OH)_2, 4H_2O$).

These all form white amorphous powders with an earthy, not saline, taste. They are insoluble in water, but the carbonate is dissolved by excess of carbonic acid. 0.3–4 G. (5–60 grs.). .0.3–4G

Effervescing Preparations.

Pulvis Effervescens Compositus (U. S. P.), Pulvis Sodæ Tartaratæ Effervescens (B. P.), Seidlitz powder.

This powder is made up in two papers, of which the blue one contains a mixture of 3 parts of Rochelle salts and one part of sodium bicarbonate, in all 10.4 G. (160 grs.), while the white paper contains 2.25 G. (38 grs. B. P.) of tartaric acid. When the powders are dissolved separately in water and the solutions mixed, the tartaric acid acting on the bicarbonate releases carbonic acid with effervescence.

Liquor Magnesii Citratis (U. S. P.) is a solution of magnesium citrate with excess of citric acid to which potassium bicarbonate is added. The whole is bottled tightly and effervesces when the cork is removed. 360 c.c. (12 fl. oz.).

Lithii Citras Effervescens (U. S. P., B. P.), a mixture of lithium carbonate or citrate with sodium bicarbonate, and citric acid (and tartaric acid, B. P.). 4–8 G. (60–120 grs.).

Magnesii Sulphas Effervescens (B. P., U. S. P.), a mixture of Epsom salts, sodium bicarbonate, tartaric and citric acids, which effervesces when mixed with water. 60–240 grs. for repeated administration; for a single administration ½–1 oz.

Sodii Sulphas Effervescens (B. P.), a similar mixture containing the sulphate of soda instead of that of magnesia. 60–120 grs. for repeated administration; for a single administration ¼–½ oz.

Sodii Phosphas Effervescens (B. P., U. S. P.), similar to the above, but containing the phosphate in place of the sulphate. Dose as for the effervescent sulphate.

Sodii Citrotartras Effervescens (B. P.), a mixture of sodium bicarbonate with tartaric and citric acids. It is not a purgative in the dose advised in the B. P. 60–120 grs.

Many other effervescent mixtures are used instead of the official ones—among them the tartrates and citrates of the alkalies, the acetate of magnesium, etc.

The sulphates of sodium and of magnesium, the tartrates of sodium and potassium and the phosphate of soda are given in solution, the last often in milk. Unless under special conditions the salts ought not to be in greater concentration than 5–10 per cent. Magnesia and magnesium carbonate are administered in powder, sweetened if necessary. The effervescent preparations are always to be taken in solution in about a tumbler of water; in some instances in which this was not understood, severe distention of the stomach with alarming symptoms have arisen from the carbonic acid being

Hunyadi - Janos + Carlsbad have MgSO4 etc
Constipation is lessened peristalsis, more resorption + hard feces. In chronic
give dilute solutions before breakfast. If acute give vegetab
a
purge night before + saline in morning = act together

freed in the stomach. The effervescent preparations ought to be kept dry, and the solution of magnesium citrate has to be kept tightly corked.

Very often the natural mineral waters are used instead of the pharmacopœial preparations, the best known purgatives among these being the Hunyadi-Janos water and Carlsbad water, which contain the sulphates of sodium and magnesium. "Carlsbad salts" are obtained by the evaporation of the waters, but are very often artificial imitations. Many other springs have the same effects, and a widespread belief exists that the natural waters are "more efficient" or "less depressant" or have some mystical virtues that are not shared in by the artificial salts, but this belief does not seem to have any real basis, and is probably a survival of the old religious belief in the healing properties of springs.

In the natural waters the purgative salts are always accompanied by other less active ones, such as the chlorides of sodium, calcium, etc.

Therapeutic Uses.—The saline cathartics are very largely used to relieve constipation. Habitual constipation seems to be caused by insufficient peristalsis, and the slow passage of the contents through the intestines allows of a more complete absorption than usual, this in turn rendering the fæces hard and dry and difficult to move onwards. The saline cathartics increase the fluidity of the intestinal contents, and thus facilitate their expulsion, and this is probably the only effect they have when taken in small quantities, and especially in dilute solution as in the natural mineral waters. In larger quantities, however, more water is retained in the bowel, and the weight and distention cause peristalsis, while in sufficient quantity they draw fluid from the blood and cause profuse watery discharges. When a very complete evacuation is desired, the saline cathartics may be given along with some of the vegetable purgatives. Such mixtures are the official Black Draught (see Senna) and the compound powder of Jalap. The saline cathartics act much more rapidly than the vegetable purgatives, and a common method of combining their effects is to give the latter in the evening and the saline the following morning.

The chronic constipation due to sedentary habits is much benefited by the saline cathartics, more especially by dilute solutions taken before breakfast. The sulphates and tartrates are harsh and unpleasant to the taste, and the natural waters are often preferred, or one of the effervescent preparations may be used in those cases.

The sulphates and tartrates are more frequently used where a single large dose has to be prescribed in order to empty the bowel, but here also the Seidlitz powder may be advised instead, as being more agreeable to the taste. These cathartics were at one time used in fever, partly from a theory that they reduced the temperature; they are certainly less liable to cause pain and griping than the vegetable purgatives, and thus tend to disturb the patient less.

The sodium phosphate is often prescribed for children, either as a powder to be given in jelly, or in solution in milk or other food, which completely hides its taste.

The saline cathartics are used to lessen intestinal putrefaction, and are sometimes very efficient, though they do not act through any anti-

$MgSO_4$ (large dose in equal vol. of water) + veg. purgative for accumulations of fluid in body due to cardiac & renal insufficiency. Diuretics + cardiac stimulants also remove fluids.
MgO or $MgCO_3$. for hyperacidity
Fresh Mg – used free. of As + acids in cases of poisoning.

septic power, but simply by removing the putrefying mass. The phosphate of soda has been especially recommended in some forms of diarrhœa in children.

The saline cathartics are administered to remove accumulations of fluid in the body arising from cardiac or renal insufficiency, or from an old effusion. For this purpose the sulphate of magnesium is used in a large dose, dissolved in about its own weight of water; if purgation does not follow in 1–3 hours, an enema may be necessary, or the saline may be given along with a vegetable purgative. This form of treatment was very popular at one time, but is liable to weaken and depress the patient, and is specially contraindicated, therefore, in asthenic conditions. Other methods of removing accumulations of fluid are by the use of diuretics (see caffeine, theobromine, page 250), diaphoretics (see pilocarpine, page 318), or by cardiac remedies (digitalis, page 357).

As diuretics the saline cathartics are inferior to other salts, such as the acetates or nitrates. Large quantities of dilute solutions of the purgative salts are of value in the treatment of some forms of obesity, the mineral waters being generally prescribed for this purpose, or the patient being sent to drink them at their source.

Magnesia and magnesium carbonate are less liable to purge than the soluble salts, and are specially indicated in hyperacidity of the stomach or in acid putrefaction in the bowel. They cause less irritation than the carbonates of the alkalies because of their insolubility, and at the same time have the advantage of acting as mild purgatives, while the lime preparations which are insoluble, tend to induce constipation. The magnesia preparations may be used also in diarrhœa as antacids, as they have no irritant action on the bowel. Freshly prepared magnesia is recommended in arsenic poisoning to form an insoluble precipitate in the stomach, and in poisoning with acids it is also of value when it can be obtained readily. In both cases it is to be given in large quantities.

The phosphate of soda has been given in various bone diseases, as in osteomalacia and rickets, this treatment being founded on the belief that the softening of the bones is due to the lack of phosphates in the food, but there is no reason to suppose that this idea is correct, and the treatment is not attended with success. It has also been recommended in the uric acid diathesis. The phosphates have been supposed to be of benefit in nervous diseases, on the theory that these were due to the insufficiency of phosphorus in the brain, and glycero-phosphates have been introduced for the same reason, but both theory and practice have proved to be erroneous, for the animal organism is unable to build up protein combinations from their inorganic constituents. The use of sulphate of sodium in phenol poisoning, which was at one time recommended, has been shown to be quite without effect on the progress of the intoxication.

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Alkalis' effect due to OH ion not to metal. —CO_3 takes H from H_2O leaving —OH, but this dissociation more delayed ~~than~~ in hydrates; the end result the same. When KOH combines with HCl, the important union is between the H + the OH which disappear, not between the K + Cl whose properties remain unchanged

Action—neutralizing acids, dissolve proteins = alk-protein, saponify fats. Salt action

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XV. HYDRATES AND CARBONATES OF THE ALKALIES.

The hydrates and carbonates of potassium, sodium and lithium owe their pharmacological action entirely to the non-metallic ion, which is so much more powerful than the metal that the latter may be discounted. In the hydrates the active constituent, then, is —HO. The carbonates and bicarbonates dissociate into K- or Na-ions and —CO_3, but the latter rapidly combines with the hydrogen of the water and thus frees —OH, so that the final effect is the same as if a hydrate had been administered, except that the carbonates are less rapidly dissociated than the hydrates, and, less —OH being formed, are less violent in their action. This hydroxyl ion, then, is what induces the alkaline reaction of the solutions and their pharmacological effect, the metallic ion only serving as a means of applying the hydroxyl ion, but not affecting the pharmacological action. In other words the alkalinity (hydroxyl ion) of the hydrates and carbonates determines their action; the metal has no practical importance.

It is therefore erroneous to take the hydrates and carbonates as typifying the action of potassium or sodium, for in these the metallic action is much less distinct than in the chlorides, the Cl ion being practically inert, while the hydroxyl is exceedingly poisonous.

It may be remarked in passing that the importance of the reaction between alkalies and acids lies not in the combination of the metal with the anion of the acid, but in the combination of the powerful hydroxyl ion with the hydrogen ion of the acid. In the effects of potassic hydrate in the stomach, the main importance is to be attached not to the potassic chloride formed, but to the water ($K—HO + H—Cl = K—Cl + H_2O$), for the potassium and chloride ions remain unchanged by the operation, while the hydroxyl and the hydrogen ions disappear.

Action.—The pharmacological action of this group is due to their powers of neutralizing acids and of dissolving proteins and changing them to alkali-proteins, and in a less degree to their saponifying fats. They have in addition the ordinary salt-action, and in concentrated solutions withdraw fluid from the tissues.

The solution of proteins by the alkalies and the characters of the compounds thus formed outside the body are well known and need

Order of solvent (protein) power — 1) OH 2) Carb. 3) bicarb. Sol. conc. so penetrate deeply & corrode. On skin dissolve corneum & sebum = cleansing, irritation & redness. Very dissolve skin = necrosis & ulcer. Mouth — alk taste, redness, soapy feel, corrosion, down to stomach — shock or cicatrices. Corrosion, in gastric ulcer or perforation

not be entered into here. The same solvent action is observed in the living tissues whenever the hydrates and carbonates come in contact with them in sufficient concentration. The hydrates are, of course, much more powerful solvents than the carbonates, and these than the bicarbonates. In very dilute solutions this solvent action is exercised only on the superficial tissues, but when stronger solutions are used, or when even weak solutions remain long in contact with the tissues, they tend to penetrate more deeply and cause widespread destruction or corrosion. These bodies form soluble compounds with the proteins and are only slowly neutralized by the tissues, so that no such barrier is raised against their penetration as is met by some other corrosives.

Applied to the **Skin** weak solutions dissolve the superficial layer of horny matter and the oily secretions of the glands, and thus cleanse the surface more thoroughly than water or solutions of neutral salts. When applied for some time, they penetrate more deeply and cause some slight irritation and redness. Concentrated solutions dissolve the skin and cause necrosis of the deeper tissues, generally covered by a semitransparent crust which falls off in the course of a few days, leaving an ulcer. The solutions of the carbonates are much less corrosive than those of the hydrates, and induce actual lesion of the skin only under exceptional circumstances, such as very prolonged application.

In the **Mouth** the hydrates and carbonates have a characteristic "alkaline" taste, and dissolve the superficial layers of the lining membrane and the mucus of the secretions. The lips, tongue, and gums assume a bright red color from the irritation and feel soapy to the touch. Concentrated solutions may cause deep corrosion, as in the skin, while very weak solutions have no effect except the characteristic taste and a reflex flow of saliva. The corrosion caused by strong solutions extends to the throat and œsophagus, and may either prove immediately fatal or may give rise to cicatrices subsequently. shock

The effect of the hydrates and carbonates in the **Stomach** has been much disputed, and even now it is impossible to explain some of the therapeutic results. Small quantities are undoubtedly neutralized by the hydrochloric acid of the gastric juice and act no longer from their alkalinity, but merely from their effects as salts, if at all. Larger quantities render the contents of the stomach neutral or alkaline and thus prevent gastric digestion. Very concentrated solutions corrode the walls of the stomach and may prove immediately fatal from causing perforation into the peritoneal cavity, while if the corrosion is not so severe, and the patient recovers from the shock and collapse, gastric ulcer and cicatrices may result.

It is very frequently stated that alkalies and alkaline carbonates induce a more rapid secretion of the gastric juice. In fact, some writers go so far as to assert that it is impossible to render the contents of the stomach alkaline except by the use of poisonous doses, because the gastric juice is so rapidly augmented by the alkalies. This belief seems to be founded on the old aphorism *contraria contra-*

No action on secretory gland of stomach i.e. acidity not augmented. Used in hyperacidity. Small doses, gastric irritant - cure bitter, eructation due to liberation of CO_2 + peristalsis increased. Mucous dissolved. As alk. neutralized less secretion, and less pancreatic juice. Medicinal doses no effe on fermentation.

riis stimulantur, which proves to have no greater basis in fact than other similar dogmas. It has been demonstrated experimentally in dogs that alkaline carbonates, whether given by the mouth or injected into the stomach through a gastric fistula, do not influence the gastric secretion, and Reichmann has recently shown that in man distilled water increases the free acid and the chlorides of the stomach contents as much as an equal amount of an alkaline solution. The only satisfactory examinations of the question, therefore, show that the alkalies have no effect whatsoever on the activity of the secretory glands of the stomach. On the other hand, they may affect the juice already secreted by making it neutral or even alkaline, and may thus render it entirely useless for digestion and disinfection. Of course in hyperacidity of the stomach, the alkalies may be of benefit by lessening the amount of free acid present.

Dilute solutions of the alkalies may act as slight irritants to the stomach wall and thus improve its circulation, and lessen pain, eructation and distention, very much in the same way as other slight gastric irritants, such as the volatile oils. In the case of the carbonates and bicarbonates, this carminative action may be strengthened by the carbonic acid liberated by the hydrochloric acid. In addition, they tend to render the mucus less tenacious, or may dissolve it completely, and thus improve the condition of the stomach. Nothing is known as to their effects on the movements of the stomach, or on its power of absorption, but if carbonic acid be liberated, it tends to increase the movements to some extent.

In the small **Intestine** the alkalies have been shown to have an indirect effect, through their diminishing the acidity of the gastric juice. The secretion of the pancreas is normally augmented on the passage of an acid fluid through the pylorus, and if the acidity of this fluid be reduced by the administration of alkalies, a much smaller quantity of pancreatic juice is thrown into the intestine. This may again render the digestion less complete, although the greater alkalinity of the intestinal contents tends to increase the efficiency of the pancreatic juice already secreted. On the other hand, in cases of hyperacidity of the stomach, the administration of alkalies may render the contents of the intestine less irritant, and thus tend to allay catarrh.

The alkalies administered in medicinal doses seem to have no effect on the intestinal putrefaction, for the double sulphates of the urine remain unchanged in amount. Kast states that very large quantities (15 G., ½ oz.) increase the putrefaction, probably through neutralizing the disinfectant gastric juice.

The alkalies have been believed to have some special action on the **Secretion of Bile**; thus, it has been supposed that they rendered the bile more alkaline and tended to dissolve the mucus contained in it, that they prevented the deposition of, and even dissolved gall-stones, or that they increased the secretion of bile and thus swept them out of the gall-bladder. All of those theories have been overthrown by

Do not increase bile or dissolve stones. Absorbed as comb with proteins & as carbonates. Presence of alk. cause less depletion of alk of fixed tissues. Flushing out of tissues by alk (salts) may increase N in urine — not due to increased metabolism.

the investigations of Stadelmann and his pupils, who have shown that alkaline salts do not increase the secretion of bile, are not excreted in it, and do not cause any change in its reaction. Any effect which the alkaline carbonates or hydrates may possess in hepatic diseases would therefore seem due to their effects in the duodenum.

The prolonged administration of very large doses of the alkaline carbonates and bicarbonates causes chronic gastro-enteritis in animals, and may thus prove fatal to them.

The hydrates are probably **Absorbed** in combination with proteins or as carbonates. Both hydrates and carbonates disappear rapidly from the stomach and intestine, although the bicarbonate of soda is sometimes credited with some laxative action; this may not, however, be due to the same causes as in the case of the saline cathartics. The absorption of these bodies increases the available ~~alkali of the blood~~ and tissues. Even when the alkali administered has been neutralized by the gastric juice, the body is rendered more alkaline, because a certain amount of the carbonate of the blood and tissues is spared, which would normally have been used to neutralize the hydrochloric acid before it could be reabsorbed. This condition of augmented a~~lkalinity can only last a short time~~, however, as the excretory glands at once proceed to remove the excess. But this transient increase in the alkalinity of the tissues has been supposed to influence the **Metabolism** very considerably. It is found that outside the body certain bodies undergo oxidation much sooner in alkaline solution than n.s. when neutral; the example most frequently cited is pyrogallol, which combines with oxygen much more rapidly in the presence of alkalies. From this it has been surmised that an increase in the alkalinity of the fluids of the body must be followed by an acceleration of the metabolism. A large number of researches made on man and animals in regard to this point have given varying results, but tend on the whole to show that the alkalies have less effect on the tissue-change than was formerly believed. The investigators of the subject have generally confined their attention to the effects of alkalies on the products of metabolism excreted in the urine, and have found the total nitrogen excreted to be unchanged in a considerable number of instances, to be slightly increased in others, and to be diminished in a few individuals. Even in those cases in which an increase is observed in the nitrogen of the urine, it does not always indicate an increase in the nitrogenous metabolism, for the urine is often increased considerably and it is evident that the interchange of the fluids of the tissues and blood is augmented; so that the increased nitrogen of the urine is accounted for by the tissues being more thoroughly flushed out than usual by the alkalies, which act in the same way as the neutral salts. The effect of the alkalies on the total nitrogen excretion seems to vary considerably with the individual, and in one and the same person different effects have been noted from two salts which exist in the blood in the same form.

Although the total nitrogen may be little affected by the adminis-

Normall acid neutralized by tissues N as NH_3. Alk administered replaces this neutralization and that N eliminated as urea. So amt of urea up & of NH_3 down. Increased alk of blood has little effect on tissue waste. Alkali of the [illegible] rapidly as alk. salts → urine - alk for 24 hours of 15-20 G Na_2CO_3 some in 3 hours of 2-3 G. → as $NaHCO_3$

tration of the alkalies, the form in which it is combined in the urine and in the blood may be changed. The ammonia of the urine is often diminished in amount, while the urea excretion is correspondingly augmented. This is especially marked in cases in which excess of acid is formed in the tissues or absorbed in any way, and is explained by the fact that this acid is ordinarily neutralized by the formation of ammonia in the tissues (see Acids). When, however, fixed alkali is present in sufficient amount, as when the carbonates are given, the nitrogen which would otherwise have been excreted as ammonium salts, is formed into urea.

The **Uric Acid Excretion** under the alkalies has been the subject of numerous researches, but in the great majority of these very imperfect methods of estimation have been used. In the few cases in which satisfactory methods have been employed, the results have been divergent, the uric acid being sometimes decreased and sometimes increased by the alkalies. In any case the change is trifling in extent, and no inference can be drawn as to the uric acid metabolism from it.

As regards the **Oxidation in the Tissues**, one observer found the oxygen absorbed and the carbonic acid excreted by the lungs increased by the alkalies, while another could detect no change. Another method of estimating the activity of the oxidation in the tissues has been used by Taniguti and Jawein, who both found that in man the neutral sulphur of the urine is increased by the alkalies at the expense of the acid sulphates; they interpret this as indicating a diminution of the oxidation of the tissues. On the other hand, Heffter and Harnack, using the same method, came to the conclusion that the oxidation in the tissues of the dog is increased by the alkalies, and this accords with Munk's observation that a diminution of the alkalinity of the blood of the horse lessened the oxidation of phenol.

The only conclusion which seems admissible from these laborious investigations is that the tissue waste is but little affected in amount by the increased alkalinity of the blood and the slight changes observed may vary not only in different species, but in different individuals, and even in the same individual at different times. The cause of this individual variation may be differences in the amount of acid formed in the tissues, but may also be differences in the local effect of the alkalies in the alimentary tract.

The organism rapidly frees itself from the excess of alkali by **Excreting** alkaline salts. This excretion occurs chiefly in the urine, which becomes less acid, or even alkaline in reaction, and in the latter event contains bicarbonate of potash or soda. As a general rule, the urine soon regains its acidity, but when fairly large doses are given repeatedly, its action may be kept alkaline constantly. This is almost always accomplished in man by the administration of about 10–15 G. (160–240 grs.) of sodium carbonate in twenty-four hours, but some persons require a still larger quantity, while others require much less. A temporary alkaline reaction lasting 2–3 hours may often be induced by a single dose of 2–3 G. The alkalies have the same effect on the

Isolated organs in alk – increase then decrease of activity –
ciliated tissue increased

Alkali (strong sol) kills all living tissue by contact.

excretion of the salts in the urine as the neutral salts—large doses increase the sodium, potassium and chlorides of the urine.

The injection of alkaline carbonates into the blood induces a more active secretion from the bronchial mucous membrane, according to Calvert, while Rossbach found it to have the opposite effect. It is questionable whether the alkali is excreted here.

The blood of rabbits treated with alkalies is said to be more strongly germicidal than usual, and these animals show greater resistance to infection with anthrax bacilli. These effects are not due to the increased alkalinity of the blood directly, for serum is not rendered more bactericidal when alkali is added to it in test-tube experiments.

When dilute alkaline solutions are applied to **Isolated Organs**, they generally increase their activity for a time, but subsequently weaken it, while strong solutions are immediately poisonous. Thus the ciliary movement of epithelium is accelerated by dilute alkalies, the sodium salts acting more strongly than the potassium because of the poisonous K-ion of the latter. The developing ova of sea urchins divide more rapidly in very dilute alkaline media, but the resulting cells are often irregular in shape. The heart also contracts longer and more strongly when it is perfused by a chloride of sodium solution rendered alkaline by carbonate of soda than when the solution is neutral. Somewhat stronger solutions increase its tonus and eventually cause systolic standstill. The arteries are contracted in the same way by contact with alkaline solutions, and are dilated when acids are perfused through them. Some of the secretions have also been found to be increased by the presence of alkalies, thus the glands of the frog's skin are stimulated by very dilute alkaline solutions. Loeb has recently observed that the presence of the —OH ion causes frog's muscle to absorb considerable quantities of water from a dilute salt solution, while on the other hand, Hamburger states that the addition of small quantities of alkalies to the drawn blood reduces the size of the blood cells. Zoethout states that some unicellular organisms prove much more resistant to the effects of the withdrawal of oxygen when they are placed in a slightly alkaline medium, and suggests as an explanation that the alkali antagonizes some poison formed during asphyxia.

Strong alkaline solutions destroy all living tissues with which they come in contact.

PREPARATIONS.

✓ POTASSII HYDROXIDUM (U. S. P.), POTASSA CAUSTICA (B. P.) (KOH), potassium hydrate, caustic potash—dry, white pencils or fused masses, deliquescent in the air and very caustic.

✓ *Sodii Hydroxidum* (U. S. P.) (NaOH), sodium hydrate or hydroxide, caustic soda—white translucent pencils, deliquescent in the air and very caustic.

5% .6-2cc dilute. *Liquor Potassii Hydroxidi* (U. S. P.), *Liquor Potassæ* (B. P.), solution of potassium hydrate, about 5 per cent., 0.6–2 c.c. (10–30 mins.), to be well diluted.

1 cc *Liquor Sodii Hydroxidi* (U. S. P.), a solution of sodium hydrate in water, about 5 per cent., 1 c.c. (15 mins.), well diluted.

.3 - 2 G POTASSII CARBONAS (U. S. P., B. P.) (K_2CO_3), a white granular powder of alkaline reaction, soluble in one part of water. 0.3–2 G. (5–30 grs.).

.3 - 2 G SODII CARBONAS (B. P.) ($Na_2CO_3 + 10H_2O$), colorless crystals with an alkaline reaction and taste, soluble in about one part of water. 0.3–2 G. (5–30 grs.).

Sodii Carbonas Exsiccatus (B. P.), sodium carbonate deprived of most of its water of crystallization, a loose, white powder resembling the ordinary carbonate in its reactions and solubility. 0.3–1 G. (5–15 grs.).

Sodii Carbonas Monohydratus (U. S. P.) ($Na_2CO_3 + H_2O$), a white crystalline powder without odor and strongly alkaline. Dose, 0.25 G. (4 grs.).

Dose of all 0.3 – 2 G. Ext to remove growths – deliquescent – wash with vinegar afterwards. Irritant in a bath – removes horny epidermis. Relief in itching skin diseases – as paste.
In hyperacidity relieve pain & eructation – with meals

Potassii Bicarbonas (U. S. P., B. P.) ($KHCO_3$), colorless, transparent crystals with a saline, slightly alkaline taste and soluble in three parts of water. 0.5–2 G. (10–30 grs.). 1/2 – 2 G 1:3

Sodii Bicarbonas (U. S. P., B. P.) ($NaHCO_3$), a white, opaque powder, with a cool, alkaline taste, soluble in 11 parts of water at 15° C. 0.3–2 G. (5–30 grs.). 0.3 – 2 G

Trochisci Sodii Bicarbonatis (U. S. P., B. P.).

Sodium bicarbonate is contained in the Mistura Rhei et Sodæ (U. S. P.).

Lithii Carbonas (U. S. P., B. P.) (Li_2CO_3), a light, white powder with an alkaline taste, soluble in 80 parts of water, but more soluble in carbonic acid water. 0.2–0.6 G. (3–10 grs.).

The preparations of magnesia and magnesium carbonate (see p. 544) are prescribed more as antacids than as cathartics, and might be included in this list. 0.3 – 4 G

Numerous alkaline mineral waters are used instead of the pharmacopœial preparations, but as a general rule they contain only very small quantities of the carbonates, and perhaps act more through the large amount of water than through their alkaline reaction.

Therapeutic Uses.—The caustic alkalies are used **Externally** to a limited extent to remove growths, such as warts, from the skin. For this purpose the potash pencils are employed, but they are very deliquescent and it is therefore difficult to limit their action to one spot, and to the superficial tissues. When the desired extent of cauterization has been obtained, the part should be washed with water, or with vinegar or some other dilute acid. The carbonates are also used externally to some extent, chiefly in baths, which they render more irritant to the skin, and in which they tend to soften and remove the superficial horny layers of the epithelium more than ordinary water or solutions of the neutral salts. The carbonates are also applied in strong solution or as a paste in itching skin diseases, and often give relief.

Internally the alkaline carbonates and more rarely the solutions of the hydrates are used for their effect on the stomach, and in cases of hyperacidity relieve the pain and eructation almost instantly. Even where no excessive acidity exists, the alkalies are often beneficial in small quantities, removing the distension and discomfort without apparently altering the digestion to any marked extent. The bicarbonate of potash is more frequently used for this purpose than the others, and the carbonic acid liberated in the stomach may be of importance in the action. Whatever preparation be used, it ought to be well diluted to avoid the irritant action on the stomach wall. Instead of these alkalies the carbonate and oxide of magnesium may be employed in powder, and possess the advantage of not causing any irritation and at the same time have some aperient action. In cases of hyperacidity the alkalies (antacids) are often given after meals, while when the secretion does not seem to contain an excessive amount of acid they are advised before meals, and may then be combined with other stomachics, such as bitters or volatile oils.

The alkalies are also administered for their effects after absorption, and here the bicarbonate of potash is most frequently prescribed,

$KHCO_3$ used for effect after absorption – neutralizes acids but does ^ increase oxidation. Of vague benefit in gout & rheumatism – mineral waters better.

while the hydrate solutions are rarely used.[1] Diabetes was formerly treated in this way, in the hope that the oxidation in the tissues would be increased, but there is little reason to suppose that the alkalies have any such effect on the metabolism, and it is now generally accepted that diabetes is not due to a general inability of the tissue to oxidize. Experience too has shown that the glycosuria is not lessened appreciably by the use of the alkalies. When, however, diabetes induces an increased acid formation in the tissues, as is almost invariably the case in its later stages, the alkalies are of undoubted benefit in neutralizing the oxybutyric acid formed and thus economizing the alkalies of the blood. In diabetic coma, temporary improvement may very often be attained by the use of large doses of alkalies.

In gout, rheumatism and the "uric acid diathesis" generally, the alkalies have been used very extensively, partly in the hope that the supposed increased combustion in the tissues would destroy a larger amount of the uric acid, and partly with the idea that the uric acid being neutralized in the tissues, would be excreted more easily and would have less tendency to be deposited. There are some grounds for believing that the alkaline carbonates are of benefit in gout and rheumatism, but neither of these theories seems sufficient to explain their effects, for no increase in the oxidation has been shown to occur, and on the other hand the uric acid is not rendered more soluble in the blood or urine by the quantities of alkali used in therapeutics. In the present position of the uric acid question and of the pathology of these diseases, however, it is futile to attempt to explain their therapeutics, though it may be surmised that the alkalies may influence the formation of the uric acid rather than its excretion. The sodium and potassium salts have been used very largely, and the lithium carbonate has been advised on the ground that lithium urate is about four times as soluble as sodium urate. Lithium has also been administered in the form of the benzoate and salicylate in these diseases, in order to combine the solvent action of the base with the effects of these acids, but, as in so many other similar attempts, one of the chief factors in the action has been lost sight of; much too small quantities of the lithium compounds have been given to affect the reaction of the blood, and besides the salicylate and benzoate do not alter it at all, as they are neutral salts. These lithium compounds therefore seem to be superfluous in the treatment of these diseases. More benefit is derived from the treatment of gout and rheumatism by the alkaline mineral waters than by artificial preparations, and this is especially marked when patients are sent to the mineral springs. The alkalinity of most of the waters is very slight, and the conclusion is inevitable that the curative agency is not the alkalinity, but the large amount of fluid taken, together with the dietetic and other hygienic conditions.

The alkaline preparations are also largely used for their effects in the urine. In cases of excessive acidity of the urine leading to pain and straining during micturition, the symptoms are relieved by these

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[1] The acetates, citrates, etc., may also be used for this purpose (p. 557).

decreases acidity of urine, & renders mucous of an irritated bladder more sol.
In gravel, given to increase amt of urine — urates hardly sol in ther.
med. doses, & phosphates tend to form. So calculi not removed. Might
dissolve contained mucous & thereby break them down. Lessen duodenal
irritation in

jaundice & stone.
By hypo = sloughing. 1:10,000 of $NaHCO_3$ in normal saline injections. Mg as acid antidote
in poison.
Vinegar the acetic.
Not stomach tube.

drugs rendering the fluid less irritating, and this relief is especially marked in irritable conditions of the bladder and urethra. They may also be of value in those cases by rendering the mucus more soluble in the bladder. In gravel the alkalies also give relief, and this has been attributed to their dissolving the uric acid in the urine, or rather to their keeping it in solution in the form of salts. In order to attain this, the urine would have to be rendered alkaline, or at least neutral, and relief is given by quantities of the alkalies which are quite insufficient to do this, so that it seems more probable that the effects are due to their increasing the amount of the urine, and thus rendering it more dilute than to their actually neutralizing the uric acid. Attempts have even been made to dissolve calculus in the bladder or in the kidney by treatment with the alkalies, but there is no question that this is hopeless. The solution of the alkalies formed in the urine is extremely dilute, and in fact, except under large doses, the reaction is not even constantly neutral. On the other hand, even the alkaline urates are by no means very soluble bodies, and are formed only with difficulty except in strong alkaline solutions. Again, alkaline urine is very liable to deposit phosphates in the bladder, and thus rather to increase the calculus than to diminish it. Experience has shown conclusively that the alkaline treatment does not remove calculus, although in one or two cases it is stated that soft calculi broke down into fragments under it, from the mucus which held the fragments together being dissolved. The pain and irritation of calculus may be relieved to some extent, however, from the acidity of the urine being lessened.

The alkaline carbonates are also prescribed in cases of jaundice and gall-stone, often with benefit. This is not due to their acting on the bile directly in all probability, for it has been shown that they do not affect it in the normal animal; the improvement may rather be ascribed to their lessening duodenal irritation.

Sodium chloride solution is often injected intravenously in shock and heart failure, and it is found beneficial to add a small quantity of sodium bicarbonate (1:10,000) to it. Alkaline solutions should not be injected hypodermically, as sloughing has been observed repeatedly from this procedure.

The bicarbonate of potash is often added to other expectorant remedies in the treatment of bronchial catarrh and bronchitis, and is believed to increase the secretion and render it more fluid and more easily expectorated.

The alkaline carbonates may be given as antidotes in poisoning with the corrosive acids, although magnesia is preferable, because it is less irritating to the stomach.

In cases of **Poisoning** with the caustic alkalies, the treatment consists in the administration of dilute acids, of which the organic—acetic, citric or tartaric—are the best. The first is most readily obtained in the form of vinegar. No attempt should be made to pass the stomach tube, as it is liable to pass through the corroded wall of

Piperazine has no solvent action on uric acids in any part of the body & therefore is worthless in treatment, just as is Quinic acid.

the œsophagus or stomach. General measures, such as central nervous stimulants, warmth, etc., may be taken.

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Piperazine and Quinic Acid.

Several new organic compounds have been introduced of late years as solvents of uric acid in the tissues and urine. The best known of these is *piperazine* or diethylendiamine ($NH<\begin{smallmatrix} CH_2-CH_2 \\ CH_2-CH_2 \end{smallmatrix}>NH$); *lycetol* and *lysidine* are nearly related bodies. The latest remedy is *quinic acid,* $C_7H_{12}O_6$, which is found in cinchona bark and in other plants; its combinations with lithium citrate, urotropine and piperazine are known as *urosin, chinotropine* and *sidonal.* Piperazine and its allies dissolve uric acid readily in the test-tube, much more rapidly than lithium or borax, which are often prescribed for their solvent action; it was therefore hoped that these bases would prevent the deposit of uric acid in the body in gout by forming soluble urates, which would be eliminated in the urine. But very little of the piperazine ingested reappears in the urine, and this quantity is too small to have any solvent action on the uric acid. And what does escape in this way is in combination with the stronger acids and not with the uric acid. When the kidneys are inflamed and necrosed in birds through the action of chromic acid, the uric acid, which would normally be excreted by the kidney, is deposited in various organs, but this does not occur except in the kidney if piperazine is administered. This has been used as an argument in support of the treatment of gout with piperazine, and some clinicians have had very favorable results from it, while others have been disappointed. It is said to relieve the discomfort due to the passage of gravel in some cases, while failing in others, but it has not been shown to be of any value in the treatment of calculus, and the urine of patients treated with piperazine has no more solvent action on uric acid than normal urine. Piperazine seems to induce no symptoms in man or animals even when administered in large quantities.

Quinic acid has been suggested as a treatment for gout on the theory that it would combine with glycocoll in the body and thus prevent the formation of uric acid, a theory based on most unsatisfactory grounds. As a matter of fact it has no effect whatever on the amount of uric acid excreted. In short, there is every reason to believe that these new remdies will prove no more reliable than the older treatment of gout and the "uric acid diathesis."

Piperazine is given in solution in doses of 1 G. (15 grs.).

Salt action before absorption. Carbonate after. Rapidly oxidized [illegible] Alkalinity of blood + urine increased as by carbonates. Butyrate intravenously = slight narcosis. [illegible] Butyrates + lactates limit N waste (take place of chohydrates. Acetates - diuretic + for gout & rheumatism. - will not neutralize gastric juice as alk carb n bicarb will, + by dil. salt action avoided. Purgative of citrates if large enough dose

XVI. THE ACETATE SERIES.

As far as their immediate effects are concerned, the acetates of the fixed alkalies resemble the chlorides, owing any effect they possess to the salt-action. In the tissues, however, the acetates are oxidized and form carbonates, so that the effects are those of the chloride before absorption, and those of the carbonate subsequently. They are probably partly decomposed by the hydrochloric acid in the stomach, and in the intestine they are rapidly absorbed. The oxidation seems to proceed rapidly, and is very complete, over 95 per cent. of the acetate disappearing, and only some 2–3 per cent. being excreted unchanged in the urine. The alkalinity of the blood and of the urine is increased by the acetates as by the carbonates, and the amount of urine is increased.

The acetates seem almost devoid of specific action—they act only as salts by changing the physical properties of the body fluids or as alkalies after absorption. The other members of the acetate series have some action, however, for the formate, propionate, butyrate and valerianate of soda have been shown to be very weak narcotics when they are injected hypodermically or intravenously; this is especially marked in the case of the butyrate. Rather more of the formate escapes unchanged in the urine than of the acetate, while the others are apparently entirely oxidized. The butyrate differs from the acetate in being capable of taking the place of the carbohydrates and fats more completely, and in thus leading to an economy of the nitrogenous tissues of the body.

All of the simpler salts of this series are equally rapidly absorbed from the intestine, but the œnanthylate and the caprylate resemble the saline cathartics in being very slowly absorbed.

The **Lactates** resemble the acetates in being almost entirely inactive, but they are rather more slowly absorbed than the acetates. They are oxidized in the tissues for the most part, and resemble butyrates in limiting the nitrogenous waste, at any rate when they are given in moderate quantities. Lactic acid is also excreted in the urine, however, in considerable quantity.

Preparations.

Potassii Acetas (U. S. P., B. P.), a crystalline salt of pleasant, saline taste and very soluble in water. 1–4 G. (15–60 grs.). 1-4 G

Sodii Acetas (U. S. P.) resembles the potassium salt.

Acetate of potash has been largely used as a diuretic and in the treatment of gout and rheumatism. It acts here exactly as the alkaline carbonates and bicarbonates, but has the advantage of not neutralizing the gastric juice, or in any way affecting the digestion except from its salt-action, which may be minimized by exhibiting it in dilute solution.

The citrates of the alkalies may be used for the same purpose, as they are not cathartic except in large quantities. (See Saline Cathartics, p. 543.)

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XVII. AMMONIA AND CARBONATE OF AMMONIA.

Ammonia solution and carbonate of ammonia differ considerably from the corresponding hydrates or carbonates of the fixed alkalies in

Gas off freely, so penetrates deeper than fixed alk., & is less lasting.
Skin = rubefacient → corrosion. Blisters rather than sol. of epidermis (as fixed alk.)
Inhaled reflex v. const. & pressure up. Resp. held then deep & full. Not absorbed
by lungs but dangerous [illegible] than infl.-asphyxia
due to swelling of glottis etc. Absorbed → urea, & blood not alk. as by fixed alk.
Arom. Spirit NH_3 = alc., vol. oil, NH_4, NH_4CO_3 → 1-4 cc in water.

their effects. The gas evaporates rapidly from its watery solutions, and the carbonate gives off ammonia freely, so that the effects are very similar, although the solution of ammonia is much the more powerful. Owing to its volatility, ammonia penetrates more rapidly and deeply than the fixed alkalies, and at the same time is less corrosive and less enduring in its effects. Applied to the skin in concentrated solution, it may corrode to some extent, but ordinary dilute preparations act merely as rubefacients, like the volatile oils. Even concentrated solutions do not dissolve the epidermis like the fixed alkaline hydrates, but tend to penetrate through it and raise blisters. When inhaled, the irritation of the nasal mucous membrane causes a reflex stimulation of the vasomotor centre, and consequent contraction of the arterioles and augmented blood-pressure, while the respiration is first arrested, and then becomes deeper and fuller. The heart may be temporarily slowed by inhibitory reflexes. Three parts of ammonia in 10,000 of air cause sneezing, pain in the nose and tears, when inspired by man, and 5 parts in 10,000 are dangerous when inhaled for some time (Lehmann). Ammonia is not absorbed by the lungs, and the symptoms arise only from the local irritation and subsequent inflammation.

Concentrated solutions cause corrosion of the mouth, œsophagus and stomach similar to that seen in poisoning with the fixed alkalies, but some of the vapor, passing into the respiratory passages, often sets up spasm of the glottis, or such swelling of the mucous membrane of the larynx and trachea as to induce asphyxia. In cases of ammonia poisoning, therefore, the symptoms often arise, not so much from the gastric corrosion as from asphyxia, and death may occur very suddenly from this cause. The carbonate of ammonia, when swallowed, also causes slight gastric irritation, and in larger quantities nausea and vomiting.

After absorption ammonia and its carbonates are rapidly changed to urea, and thus differ from the fixed alkalies in not rendering the blood more alkaline, and in having no effect on the urine except to increase the urea and thereby cause some diuresis.

The carbonate of ammonia stimulates the central nervous system when it is injected into the blood in some quantity, but it has no such effect when absorbed from the stomach. (Cf. Ammonium Chloride, page 498.)

PREPARATIONS.

28% ✓ *Aqua Ammoniæ Fortior* (U. S. P.), a solution of ammonia in water, containing 28 per cent. of the gas by weight.

Liquor Ammoniæ Fortis (B. P.), 32½ per cent. by weight.

10% ✓ *Aqua Ammoniæ* (U. S. P.), *Liquor Ammoniæ* (B. P.), an aqueous solution of ammonia of 10 per cent. strength by weight.

✓ *Spiritus Ammoniæ* (U. S. P.), an alcoholic solution of ammonia containing 10 per cent. of the gas by weight. 1 c.c. (15 mins.).

✓ SPIRITUS AMMONIÆ AROMATICUS (U. S. P., B. P.), Aromatic Spirit of Hartshorn, Spirit of Sal Volatile, contains ammonia and ammonium carbonate along with several volatile oils dissolved in alcohol. 1–4 c.c. (15–60 mins.), in a glass of water.

1-4 cc. in glass H_2O

Vesicant where cantharides contraindicated. Liniment as rubefacient in bruises. Gas from NH_4HCO_3 in fainting. "Smelling salts" = $NH_3HCO_3 + NH_4OH$ + oil of lavender. 2 g of NH_3HCO_3 a good emetic. Good in debility, alcoholism. Also arom. spir. $NH_4HCO_3 + NH_4OH$ given mouth, intraven. or by hypo in heart failure (sudden) or collapse. Arom. spirit in all sorts of depression. NH3 in snake bite.

Linimentum Ammoniæ (U. S. P., B. P.), ammonia liniment, volatile liniment, contains about 3.5 per cent. of ammonia (2.5 per cent. B. P.).

AMMONII CARBONAS (U. S. P., B. P.) is not the pure carbonate, but a mixture of somewhat varying composition, consisting of carbonate (NH_4HCO_3) and carbamate of ammonia ($NH_4NH_2CO_2$). It releases ammonia in the air and has therefore its pungent taste and smell. It forms translucent, crystalline masses, is very soluble in water and is contained in the aromatic spirit of ammonia. 0.2–0.6 G. (3–10 grs.) in dilute solution.

0.2 - 0.6 g diluted

Ammonia is contained in several of the tinctures of the B. P. (ammoniated tinctures) and in the Linimentum Camphoræ Ammoniatum, etc.

Therapeutic Uses.—The aqueous solutions of ammonia are comparatively rarely employed, although the strong solution has been advised as a vesicant in cases of renal disease, in which cantharides is contraindicated. The ammonia solution has to be covered by a watch-glass in order to prevent its evaporation, and is said to be more painful than other vesicants. The liniment is used as a rubefacient in bruises and in other similar conditions. The gas arising from ammonium carbonate is often inhaled in cases of fainting or collapse, in order to elicit reflex stimulation of the medullary centres. The ordinary "smelling salts" used for this purpose consist of the carbonate reinforced with some of the strong solution and flavored with oil of lavender.

The aromatic spirits of ammonia and the carbonate (in solution) are used as mild gastric stimulants in debility, flatulence and alcoholism, and are very efficient for a short time. Large doses of the carbonate (2 G.) have been used as emetics, and are less depressant than many others, such as tartar emetic or ipecacuanha.

The carbonate of ammonia and the spirits or even the ordinary water of ammonia are often given in cases of collapse or sudden heart failure. They are generally administered by the mouth and probably act here not directly on the heart and respiratory centre, as has been supposed, but reflexly from gastric irritation. They have also been injected subcutaneously or even intravenously for this purpose, and here the local action may be reinforced by a direct action on the medulla oblongata. The action lasts only a very short time, but is often sufficient to tide the patient over an acute collapse. In depression from many different causes the aromatic spirits of ammonia is a favorite remedy, and probably owes its value to its gastric action, and not to any changes in the central nervous system. The carbonate is often added to other expectorant remedies to render the bronchial mucous secretion more fluid. (See Ammonium Chloride, page 498.)

Strong water of ammonia is applied locally in snake-bite and is popularly believed to be very efficacious. It has no effect on the toxalbumins of snake poison, and probably is of little or no value in these cases.

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+ not alkalinity of urine increased.!

The **Acetate and Citrate of Ammonia** act in the same way as the chloride locally, but undergo oxidation in the tissues, and the whole is changed to urea, so that the ammonia of the urine is not increased, but only the urea. The solutions are used as diaphoretics and diuretics, and are often prescribed along with more powerful remedies in fever.

PREPARATIONS.

Liquor Ammonii Acetatis (U. S. P., B. P.), spirit of Mindererus, contains about 7 per cent. of the acetate with some free acetic acid and carbonic acid and must be freshly prepared. 10–25 c.c. (2–6 fl. drs.). 10-25cc

Liquor Ammonii Citratis (B. P.) resembles the solution of the acetate. 2–6 fl. drs.

XVIII. OXALATES.

The oxalates (NaOOC—COONa, sodium oxalate) differ from the acetate series in not undergoing oxidation in the tissues and in being poisonous to most forms of living matter. This poisonous action is shown in the frog by depression and final paralysis of the central nervous system, the brain being first affected, then the medulla oblongata and spinal cord. Later still, the terminations of the peripheral nerves and the muscles and heart are paralyzed, twitching and fibrillary contractions of the voluntary muscles often being observed first.

In mammals there is apparently at first a stimulation of the medullary centres, for rapid, deep breathing occurs in the rabbit, and vomiting and nausea in the dog, and according to some observers, the arterial tension is first increased through stimulation of the vasomotor centre. Later the movements are wanting in coördination, the respiration becomes slow and dyspnœic, the heart is weak, and the animal becomes comatose and dies, sometimes in convulsions.

In cases of oxalate poisoning in man, the early symptoms are great muscular weakness, twitching of the muscles, especially of those of the face, more rarely convulsions; later there follows collapse with a weak, fluttering pulse, pallor or cyanosis, coma and death.

Oxalates are very poisonous to all forms of animal life and to plants containing chlorophyll, but are harmless to the moulds, bacteria and some algæ. They are absorbed with great difficulty from the stomach and intestine, and cause irritation and effusion of liquid except in very dilute solutions. Added to the blood outside or inside the body, they prevent its coagulation, and the rennet ferment also fails to coagulate milk in the presence of small quantities of oxalate (see Calcium). The frog's heart is very much weakened by the addition of oxalate of soda to the blood perfused through it, while the mammalian heart is not affected by very small quantities, but if the injection of oxalate be continued, becomes suddenly weaker. The action on the central nervous system has been mentioned already, and consists in depression, which is sometimes intermixed with, or preceded by symptoms of stimulation.

When the ordinary nerve-muscle preparation is soaked in oxalate solution, the same twitching and tremor of the muscle is observed as when the salt is injected into the frog. Later the nerve ends are paralyzed, and the nerve fibres lose their irritability, as is indicated by the disappearance of the electrical current of action. The muscle is extremely weak, and according to several observers, loses its irritability, while Locke finds that it can be made to contract locally by strong currents, even after being soaked for several hours. The post-mortem rigor does not seem to be prevented by oxalate as has been stated by some observers.

Oxalate solutions precipitate lime salts, and as it is well known that lime is an essential constituent of living matter, it has been suggested that the oxalates cause these changes in the organism, not through any direct action on protoplasm, but through their precipitating the calcium and thus changing its ordinary relation to the proteids. This explanation has been supported by the discovery that calcium salts added after oxalates restore the lost function in many cases, although this of course admits of the explanation that the calcium merely throws the oxalate out of solution, and does not really supply fresh lime to the tissues. The presumption is strong, however, that the action of the oxalates is due, at any rate in part, to their precipitating the calcium in the tissues, although they may have a specific action on living matter in addition.

The alkalinity of the blood was found to be much reduced by the administration of neutral oxalates (Meyer), and it has been surmised that this is because the oxidation of the tissues is retarded by the presence of oxalates in the blood. This may account for the appearance of a reducing body in the urine of animals poisoned with oxalate; it sometimes occurs in poisoning in man and is said not to be dextrose.

Practically the whole of the oxalate ingested is excreted in the urine in the form of oxalate of calcium, and the insoluble crystals are often deposited along the urinary tubules and may stop them up entirely and thus cause anuria, congestion and inflammation of the kidney; albuminuria is often the most marked symptom in slight poisoning in man. The deposits of oxalates often form white lines running from the base to the apex of the renal pyramids, which are quite evident macroscopically at the autopsy. Small oxalate calculi have also been produced in the pelvis of the kidney, bladder, or ureter through the prolonged administration of oxalate or oxamide to animals. Not infrequently these renal changes are the only lesions found post-mortem in cases of poisoning with oxalates.

The prolonged administration of oxalates to animals has been found to induce changes in the skeleton, for sheep fed on plants containing much oxalate are found to have less lime in the bones than usual, and in rabbits symptoms of rickets are said to be induced from the lessened absorption of lime.

The other members of the oxalate series, malonates ($CH_2(COONa)_2$) and succinates ($(CH_2)_2(COONa)_2$), differ from the oxalates in being very much less poisonous, the fatal dose of malonate of soda being about twenty times that of the oxalate, and the succinate being almost indifferent. The malonate is almost completely oxidized in the tissues, and succinate disappears completely. It is significant that malonic and succinic acids form much more soluble salts with lime than does oxalic acid. Both malonate and succinate of soda are absorbed only slowly from the intestine, and act as saline cathartics.

The oxalates are not used in therapeutics. In cases of oxalate poisoning the natural antidote is lime, which forms an insoluble precipitate in the stomach and may also relieve the symptoms induced by the withdrawal of lime from its normal combination in the tissues. At the same time large quantities of water and diuretics may be given in order to wash out the crystals of oxalate from the urinary tubules.

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Important as 1) more active because of acid H ion 2) because of rest of mol. Neutralize alk., ppt globulins, withdraw water. Protoplasm poisons — [illegible] is alk. or neutral; HCl of gastric juice bactericidal. H_2SO_4 (white br. bl.) HNO_3 (yel) caustic necrosis. HCl, H_3PO_4, organic, less irritant. M.M. corroded

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XIX. ACIDS.

Some acids owe their activity in the organism almost entirely to their acidity, *i. e.*, to the hydrogen ion, which is much more powerful than the potassium ion, but otherwise stands on the same plane with it; those acids may therefore be treated of together. In the case of many other acids, such as prussic or salicylic acid, the effects of the acidity or hydrogen ion are insignificant in comparison with those of the rest of the molecule or the negative ion, and these are treated along with their salts.

Action.—The acids owe their action on living tissues to their neutralizing alkalies, to their withdrawing water, when in concentrated form, and to their precipitating some of the proteins, more especially the globulins.

Most living matter is neutral or slightly alkaline in reaction, and seems to be incapable of existing in acid media. Exceptions are met with in some of the moulds and in other vegetable organisms which live in somewhat acid solutions, but even these are destroyed by more concentrated solutions, perhaps because the acids precipitate their proteins. Acids are therefore **Protoplasm Poisons** and antiseptics of some power. Hydrochloric acid is found to delay the growth of organisms, and even to destroy the great majority of the less resistant forms in 0.2–0.3 per cent. solution, or in the percentage in which it exists in the gastric juice. The others vary in strength largely according to their acidity, that is, according to the number of hydrogen ions, or the amount of dissociation.[1]

When sulphuric or nitric acid is applied to the **Skin** in concentrated form, it acts as a powerful caustic, destroying the epidermis and penetrating to some distance into the skin and subcutaneous tissues, in which it causes necrosis. This is of course accompanied by great pain, and if much of the skin is attacked, by shock and collapse and symptoms similar to those seen in severe burns. Sulphuric acid causes a white, later a brown or black eschar, nitric acid a yellow. Hydrochloric acid is less liable to cause wholesale destruction of the skin, but penetrates the epidermis and raises blisters. The organic acids and phosphoric acid are still less irritant, but cause redness and even blistering when applied in concentrated solution. Dilute solutions of the acids may act as slight irritants to the skin, and often cause a feeling of stiffness and numbness, perhaps from precipitating the proteins.

The corrosive action of the acids is much more marked when they are applied to the less resistant **Mucous Membranes.** Even small quan-

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[1] In some instances the toxicity of an acid is not proportional to its dissociation, however, and Loeb has shown that some acids, notably the slightly dissociated higher organic acids, penetrate cells more readily than some of the simpler ones and thus more than compensate for the fewness of their hydrogen ions.

G.I. — corrosion, perforation, shock death or cicatrix inanition. Tissues brittle & shrunken — (with alkali soft & swollen) Vomit, diarrhoea, rapid weak pulse, shallow resp. Vapor — spasm of glottis, oedema — asphyxia. Reflex on saliva. No increase of gastric juice. HCl best in stomach. Antiseptic. Promotes pancreatic secretion. Rapidly absorbed — in blood as salts

tities of strong sulphuric acid striking the eye are sufficient to destroy the sight.

In the **Mouth, Œsophagus, and Stomach**, the corrosive action is evidenced by complete destruction of the mucous membranes which come in contact with the strong acid. The œsophagus and stomach may be perforated, and this, along with the shock and collapse, often proves immediately fatal, or if the patient recovers temporarily, the erosions may give rise to cicatricial contractions and death from inanition. Hydrochloric acid and the stronger organic acids are capable of causing corrosion of the mucous membranes, but this is not so extensive generally as that following nitric and sulphuric acid. The corrosion from acids differs from that from alkalies, in the tissues being shrunken, hard and brittle, while after a caustic alkali they are soft and swollen and have a slimy soapy appearance.

The symptoms of corrosive acid poisoning are intense pain in the mouth, throat and stomach, vomiting and often diarrhœa, shock and collapse, with rapid, weak pulse and shallow respiration. The temperature is often subnormal and death occurs in the course of a few hours. When fuming acids are swallowed, and especially in poisoning with hydrochloric acid, the irritant vapor passing into the respiratory passages may cause spasm of the glottis, or œdema of the larynx, and prove immediately fatal from asphyxia. Even one part of hydrochloric acid vapor in 20,000 of air causes sneezing and pain in the throat and chest (Lehmann).

Dilute solutions of the acids have a characteristic taste, and induce a reflex flow of saliva and an astringent feeling in the mouth and throat from their causing a coagulation of the superficial layers of proteins. In the stomach they displace any weaker acids from their combinations with bases, and may have some antiseptic action, but do not influence the amount of secretion in any way. The gastric juice is normally acid, containing about 0.2 per cent. of free hydrochloric acid, and this acid reaction is essential to the action of pepsin. Other acids may replace the hydrochloric acid in digestion, and a good deal of work has been done in determining the relative value of the acids for this purpose. This is done by adding different acids to solutions of pepsin in test-tubes, and noting the amount of fibrin or other protein which is digested in the course of a number of hours. These experiments have shown that hydrochloric is better than most other acids, but is perhaps surpassed by hydrofluoric and oxalic acids, whose poisonous action precludes their use; so that both clinical experience and experiment point to hydrochloric acid as the most suitable acid for use in the stomach. In cases of deficient gastric secretion, the administration of acids increases the acidity of the food as it passes into the duodenum and may thus promote the formation of secretin and consequently the secretion of the pancreas.

× Not free

The acids are absorbed from the alimentary canal fairly rapidly in most cases. In the **Blood and Tissues** they do not exist as acids but as salts, for the reaction of the blood must remain slightly alkaline matter from complete (oxidation) bodies' bases — blood acid! In man NH_3 formed to fixed alk. neutralize acid — NH_3 mechanism nec. to guard against acid formed in tissues (dietetic). Herbivora depend on fixed alk. — Na_2CO_3 = recovery

throughout life, and if sufficient acid be given to neutralize the alkalies of the body, the animal dies before the blood becomes neutral, although after death it may be found to be acid. The means provided by the economy to neutralize acids differ in different animals; in the herbivora the fixed alkalies of the blood and tissues are called upon chiefly, and if more acid be absorbed than can be neutralized by these, the animal dies; in the carnivorous animals and in man, a further protective mechanism exists, for in these ammonia is liberated by the tissues, and serves to neutralize the acid, and thus saves the fixed alkalies. The difference is relative and not absolute, however, for the herbivora also develop some ammonia, and the carnivora employ some of the fixed alkalies to preserve the normal reaction of the tissues. Man appears to stand midway between the two classes, for while ammonia appears in the urine after acid absorption, the fixed alkalies are also present in excess. Much larger amounts of dilute acids may therefore be absorbed without serious symptoms by man and by the carnivora than by the herbivora. The explanation of this difference between the flesh-eating and the plant-eating animals is to be found in the nature of their food. The flesh-eaters are accustomed to the formation of some acid in their tissues, because the alkalies of their food are insufficient to neutralize the acids formed by the oxidation of the organic matter, and they would gradually be deprived of all their alkaline salts, therefore, were they not protected by the formation of ammonia. On the other hand, the herbivorous animals absorb much larger quantities of the organic salts of the alkalies in their food, and these forming carbonates in the body, serve to neutralize what acid is formed in the tissues. In ordinary circumstances, therefore, they have no need to protect the fixed alkalies, and are unprovided with any mechanism for this purpose. When an excess of acid is absorbed, they neutralize it by means of the fixed alkali of the tissues and blood, and this leads to a lessened alkalinity of the blood, which becomes unable to carry so much carbonic acid from the tissues to the lungs. Thus in acid poisoning in rabbits, the alkalinity of the blood has been found to be so greatly reduced that instead of containing some twenty-five volumes of carbonic acid per cent. of blood, it carried only two volumes per cent. or very little more than could be dissolved in the same amount of water. When this occurs, the tissues are unable to rid themselves of their carbonic acid, and a series of symptoms follow, commencing in deep, labored, rapid, afterwards shallow, respiration; the heart is weak, a condition of collapse follows, and eventually the respiration ceases, the heart continuing to beat for some time longer. The quantity required to poison a rabbit in this way is about 1 G. of hydrochloric acid for each kilogm. body weight. The injection of sodium carbonate, even in the last stage of intoxication, is followed by rapid recovery, from more alkali being supplied the blood and tissues, while other carbonates are not so useful, owing to the action of the basic ion. The blood-pressure in rabbits is much reduced by the acids, from depression of the vaso-

Salts excreted as acid salts by kid — retain as much of the alk as possible → hence irritation albumin etc. Much increase of NH3. urea about same fatty degen. On skin — loss of vitality — corrosive when alk depleted Citric. tart acid etc to quench thirst flavor to draughts — or carbonic acid w

motor centre and the heart. In carnivora and man, the absorption of dilute acids does not alter the alkalinity of the blood to any marked degree, and no serious symptoms arise from this cause.

The salts formed in the blood and tissues after the absorption of acids are rapidly **Excreted** by the kidneys, which, however, retain as much alkali as possible in the body and thus excrete the salts in an acid form. Hence there arises in some cases irritation of the kidneys, with albumin, and even blood, in the urine, which is rendered more acid than usual and causes a sensation of heat and smarting in the bladder and urethra. In the herbivora the reaction changes from alkaline to strongly acid, and large quantities of the salts of the alkalies appear, while in the carnivora some increase in the sodium and potassium of the urine occurs along with a much greater increase in the ammonia. The total nitrogen is somewhat increased from the large amount of ammonia, but the urea is slightly decreased. Some authors have found an augmented excretion of lime in the urine, while others state that it is less than usual.

Not infrequently fatty degeneration of the heart, liver, muscles or kidney has been observed in corrosive acid poisoning, when the patient survived for a few days, and Fraenkel and Reiche found a form of necrosis of the renal cells in these cases. These changes are not due to free acid in the blood, but their exact cause has not been satisfactorily determined.

The prolonged treatment of animals with acids has been found to be followed by anæmia and loss of flesh and strength, which are probably attributable to the disturbance of the digestion and not to any specific action of the acids.

Acids applied directly to the living tissues lessen their vitality, and unless there is sufficient alkali present to neutralize them, soon destroy it entirely. In some cases they tend to cause a temporary increase in activity at first; thus the cilia of ciliated epithelium have been found to move more rapidly at first in very dilute acids and then to cease all movement, while muscle seems to be rendered weaker and less irritable at once. As in the case of alkalies, Loeb finds that dilute acid causes muscle to imbibe more water than salt solution does, and Hamburger finds that the red blood cells are increased in size by the addition of small quantities of acid to the blood outside the body. The frog's heart is weakened and dilated by the addition of acid to a perfusing solution, and the muscular wall of the vessels also relaxes. The addition of acids to the blood tends to agglutinate the red cells and to form methæmoglobin.

Therapeutic Uses.—The acids are used in medicine only to a limited extent, and most of the official preparations might well be dispensed with.

They may be employed to give flavor to draughts in fever and in the thirst of diabetes, the most popular forms being those formed from fruits, such as lemons, limes, or grapes. The taste is due to the sugars, acids and volatile oils of the fruits, and is modified by the presence of inert colloid substances, such as the pectins. The acids, of which citric, tartaric and malic are the chief, are very important factors in the effect, for if these be neutralized, the fruit juices become insipid, and do not quench thirst so thoroughly. The so-called grape cure, in which very large quantities of grapes are eaten, owes most of its value to the large amount of water taken, although the acids and

hypochlorhydria dyspepsia, sedentary, convalescence.
In alk poison – acetic & vinegar & other organic a. diluted & thru glass tube. Styptic. Corrosive – for tumors. In poisoning give insol Mg

MgO, Lime from walls, chalk, soap, wood ashes. dil. Protect with milk, egg white

salts may act as aperients in the same way as the saline cathartics. Instead of the fruit juices, carbonic acid waters may be advised, and occasionally other acids, such as phosphoric or sulphuric, are prescribed to give flavor.

Acids are also used in certain forms of dyspepsia in which the hydrochloric acid of the stomach is deficient. Hydrochloric acid is most frequently prescribed for this purpose, although nitric and nitro-hydrochloric acids have also some reputation; the hydrochloric acid is certainly more efficient than these in test-tube experiments on digestion. The forms of dyspepsia thus treated are generally those arising from a sedentary life or in the course of convalescence, and the acids are often prescribed along with the bitter stomachics and are to be taken about half an hour before meals. Irritation of the stomach, or hyperacidity of the gastric juice, is, of course, a contra-indication.

In cases of alkaline poisoning, the acids are the natural treatment; the organic acids should be preferred for this purpose, as they are less liable to cause additional corrosion, and acetic acid in the form of vinegar is more likely to be at hand than any other.

In every case in which acids are prescribed internally, they have to be given largely diluted, as otherwise they irritate the throat and stomach. They are taken through a glass tube, in order to prevent as far as possible their action on the teeth.

Strong acids have some effect in arresting hæmorrhage (styptics) when applied directly to the bleeding point, but are much inferior to some of the metallic salts, such as the iron perchloride.

Externally, the acids are used to some extent as corrosives, strong nitric acid being not infrequently used to destroy small tumors, to cauterize the os uteri and for similar objects. Its action is more easily localized than that of potash and on the other hand is more powerful than the metallic salts, such as silver nitrate and zinc chloride. In dilute solution, they are sometimes applied to the skin to lessen excessive local sweating and diluted vinegar is often used to sponge fever patients.

In cases of corrosive **Poisoning** with acids, the first indication is to neutralize the acids as far as possible by giving alkalies. These ought not to be in themselves corrosive, and the best antidote is therefore the insoluble magnesia and magnesium carbonate. Lacking these, the most readily accessible alkali is the best, and the lime may be scraped from the walls or ceilings, or chalk, soap, or wood ashes may be given. The walls of the stomach and œsophagus may also be protected by giving milk or white of egg, or the acid may be rendered less corrosive by diluting it with large quantities of water.

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H_2SO_4 eq. Conc HNO_3 on glass rod for caustic action
HCl less corrosive - blister - white. Dose of dil acids 0.6 - 2 cc

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Compare Alkaline Hydrates and Carbonates.

For the specific effects of the anions of the acids, see chlorides, phosphates, acetates, oxalates, etc.

Sulphuric Acid.

Sulphuric is one of the most corrosive acids when it is applied in concentrated form, and often induces complete charring of the tissues, and a coal-black slough.

Acidum Sulphuricum (U. S. P., B. P.) concentrated sulphuric acid, containing at least 92.5 per cent. by weight of absolute sulphuric acid U. S. P., containing 98 per cent. B. P.

Acidum Sulphuricum Dilutum (U. S. P., B. P.) contains 10 per cent. U. S. P., 13.65 per cent. B. P. of absolute sulphuric acid. 0.6–2 c.c. (10–30 mins.). 0.6-2 cc

Acidum Sulphuricum Aromaticum (U. S. P., B. P.) is an alcoholic solution flavored with ginger and cinnamon. The U. S. P. preparation contains 20 per cent., the B. P. preparation 13.8 per cent. of sulphuric acid. 0.3–1 c.c. (5–15 mins.) in a glass of water.

Sulphuric acid and its preparations are not largely used. It is occasionally applied as a caustic, but nitric acid is generally preferred. Internally it is largely used as a prophylactic and remedy in lead poisoning, but it is probably of little value here. When prescribed internally the aromatic acid is the best form, but sulphuric acid could be dispensed with entirely in therapeutics.

Nitric Acid.

Nitric acid is equal or superior to sulphuric in its corrosive action. It stains the skin and tissues a bright yellow or yellowish-brown, and this serves to distinguish cases of poisoning under the two acids.

Acidum Nitricum (U. S. P., B. P.) contains 68 per cent. of absolute nitric acid (HNO_3) (B. P. 70 per cent.).

Acidum Nitricum Dilutum (U. S. P., B. P.) contains 10 per cent. U. S. P., 17.44 per cent. B. P. by weight of absolute nitric acid. 0.6–2 c.c. (10–30 mins.). .6 - 2cc

A glass rod dipped in concentrated nitric acid is used as a corrosive. The dilute acid has been advised in dyspepsia, but is generally considered inferior to hydrochloric acid, and has been shown to be much less efficient in artificial digestion. It has also some reputation in certain liver diseases, but is supposed to be inferior to the nitrohydrochloric acid. Nitric acid is occasionally used in some intestinal conditions accompanied by diarrhœa.

Hydrochloric Acid.

Hydrochloric acid is less corrosive than the two preceding acids, and tends to cause blistering on the skin rather than necrosis. It may cause actual loss of substance, however, when applied to the mucous membranes in concentrated form, and stains the mouth a whitish color.

Acidum Hydrochloricum (U. S. P., B. P.), muriatic or hydrochloric acid, contains nearly 32 per cent. by weight of the gas HCl.

Acidum Hydrochloricum Dilutum (U. S. P., B. P.) contains 10 per cent. of hydrochloric acid gas. 0.3–2 c.c. (5–30 mins.) in a glass of water. .3 - 2cc

Concentrated hydrochloric acid is scarcely used in therapeutics. The fermentation). Peristalsis increased. Aqua regia's rep. in hepatitis ill-founded. H_3PO_4 less irritant. Tissues can't form P comp from inorganic.

diluted acid is often prescribed in dyspepsia in which there seems to be a deficiency of the natural acid secretion. In cases of diarrhœa in which excessive putrefaction of the intestinal contents is present, it may be of benefit when prescribed along with other drugs; this action is probably explained by its disinfecting the stomach contents, as the hydrochloric acid of the gastric secretion normally does; for the double sulphates of the urine certainly diminish under its use in many cases. It is said that hydrochloric acid prevents the lactic fermentation in 1:1,000 dilution, and that in addition to its action on the digestive ferments it increases the peristalsis of the stomach.

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Nitrohydrochloric Acid. Aqua Regia

Nitrohydrochloric acid is formed by mixing hydrochloric and nitric acid, and contains not only the original acids, but a number of decomposition products, such as chlorine, nitroxychloride (NOCl) and nitrous acid. The strong acid (aqua regia) is the most powerful solvent and oxidizing agent known, dissolving such refractory metals as platinum and gold.

Acidum Nitrohydrochloricum (U. S. P.), nitromuriatic acid, aqua regia, is formed by mixing 180 parts of nitric acid with 820 parts of hydrochloric acid.

Acidum Nitrohydrochloricum Dilutum (U.S.P.) is formed by mixing 40 c.c. of nitric acid with 182 of hydrochloric and diluting the whole to one litre. 1 c.c. (15 mins.). 1cc

Acidum Nitrohydrochloricum Dilutum (B. P.) is formed by mixing 6 parts of nitric acid and 8 parts of hydrochloric acid with 50 of distilled water. 5–20 mins.

The diluted acid alone is used in therapeutics, and does not seem so efficient in ordinary dyspepsia as the dilute hydrochloric acid, but has some reputation in the treatment of liver diseases and jaundice, though no explanation of its action in these conditions has been offered. The acids cannot act as such except in the alimentary canal, but in the nitrohydrochloric acid other constituents, such as chlorine, are present, and it is conceivable that some of these may have a specific effect on the liver; further proof would seem to be required, however, that the treatment is really of value. The acid is ordinarily given by the mouth, but some authorities advise that it be applied in the form of a foot-bath or of an ordinary bath, and others apply it in a compress over the liver. These external applications are stated to be even more efficacious in hepatitis than the internal administration, and this serves only to strengthen the doubt of the value of the remedy, for it is contrary to all experience that such bodies should be absorbed in any quantity from the skin, and their local action as cutaneous irritants does not differ from that of other drugs.

Phosphoric Acid.

Phosphoric acid is much less corrosive and irritant than the other mineral acids, but in large, concentrated doses may cause gastro-enteritis.

Acidum Phosphoricum (U. S. P.) contains 85 per cent., *Acidum Phosphoricum Concentratum* (B. P.), 66.3 per cent. of absolute phosphoric acid (H_3PO_4).

.3–2cc *Acidum Phosphoricum Dilutum* (U. S. P., B. P.) contains 10 per cent., U. S. P., and 13.8 per cent., B. P., of phosphoric acid. 0.3–2 c.c. (5–30 mins.).

Phosphoric acid has been used to some extent to form cooling draughts in

H_2SO_3 - reducing - when oxidized very poisonous. S burned in air tight rooms 20 hrs for disinfection. The gas fairly (only) germicidal. Bleaches coloring matters. Fumes fatal. In tissues to sulphates 'in presence of moist. Anhydride very irritant to resp. tract.

fever. It has also been prescribed in various cachectic conditions on the theory that these were due to a deficiency of phosphates in the food and tissues; but it has never been shown to be of any benefit, and experiments have proved that the animal tissues are unable to build up phosphorus compounds from the inorganic phosphates.

Sulphurous Acid.

Sulphurous acid differs from the preceding members of the group in its powerful reducing action, through which it becomes oxidized to sulphuric acid, and which renders it strongly poisonous to protoplasm in general, quite apart from its acidity. Sulphurous acid anhydride is accordingly used to a considerable extent to disinfect rooms and furniture after infectious diseases; for this purpose sulphur is burned in the room, which ought to be rendered as air-tight as possible, and the fumes are allowed to act for several hours before the room is ventilated. The value of this method of disinfection has been called in question, but there is no doubt that sulphurous acid gas is fairly germicidal when it is applied along with moisture. It is not capable of such a wide application as formaline, because sulphurous acid bleaches many coloring matters, and the procedure is open to the objection that it may lend a sense of security which is quite unwarranted, and may lead to the neglect of other measures. The disinfection to be of any value must be thoroughly carried out, and can only be applied to inanimate objects, as the fumes are fatal to the higher animals, even when much less concentrated than are necessary to destroy bacteria. In order to be of service, at least one volume of SO_2 ought to be present in each hundred volumes of air, and even this concentration is insufficient to destroy the spores of bacteria. Novy[1] recommends 3–6 pounds of sulphur to be burned for each 1,000 cubic feet of space; the walls and floor should be sprayed with water, and the room must be kept perfectly closed for at least twenty hours.

The chief symptoms of poisoning with sulphurous acid are those of irritation of the mucous membranes, and if the solution be swallowed these may not differ from those of the other acids. Sulphurous acid penetrates the tissues more rapidly than most of the others, owing to its gaseous form, and does not cause actual loss of substance as sulphuric acid does.

In poisoning from the inhalation of the anhydride, on the other hand, the symptoms arise chiefly from the respiratory tract. Even in five parts in 10,000 it acts as an irritant, causing sneezing, coughing and lachrymation, and in somewhat greater concentration it becomes entirely irrespirable; still smaller quantities in the air cause bronchial irritation and catarrh, when inhaled for some time. Sulphurous acid is neutralized and oxidized for the most part to sulphates in the tissues, or probably partly in the course of absorption.

The solution of sulphurous acid of the pharmacopœia is used to a limited extent as an antiseptic solution in skin diseases. It is

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[1] *Novy and Waite.* Medical News, lxxii., p. 641.

Organics less corrosive. Urine blood not acid as salts → carbonates. Acetic. – blistering, congestion. Int – – death. To skin as irritant in contusions. Vinegar styptic, whole v.m. centre in fainting, [illegible] for epistaxis, formic & lactic ng.

more irritant to the broken skin than many other equally powerful antiseptics.

[illegible] in skin tissues

Acidum Sulphurosum, U. S. P.—A solution of not less than 6.4 per cent. by weight of sulphurous acid gas (SO_2) in water. B. P., a solution containing 6.4 per cent. of hydrogen sulphite (H_2SO_3) corresponding to 5 per cent. by weight of sulphurous anhydride (SO_2).

Organic Acids of the Fatty Series.

The organic acids have a much less marked local action than the inorganic, causing little or no corrosion unless when applied to mucous surfaces in very concentrated form. They are absorbed as salts of the alkalies, but do not as a general rule reduce the alkalinity of the blood or render the urine more acid, because they are oxidized to carbonates in the tissues. Oxalic acid is the chief exception to this rule, but the specific action of the oxalates is powerful enough to conceal the acid action to a great extent.

Acetic Acid applied in concentrated solution to the skin causes irritation and congestion and eventually blistering, but does ~~not induce necrosis except of the most superficial layers.~~ The congestion is often followed by marked pallor instead of by blistering; and this has been explained by contraction of the vessels, but may be due to a precipitation of the proteins of the skin. In the mouth and stomach it acts as an irritant, causing vomiting, great pain, collapse and even death; the epithelium is found thickened and occasionally contains hæmorrhages. Dilute acetic acid (vinegar) has little effect apart from its acid taste, and is used largely as a flavoring agent and condiment. The prolonged use of large quantities may, however, give rise to gastric irritation and to loss of appetite and weight.

Acidum Aceticum Glaciale (U. S. P., B. P.) ($HC_2H_3O_2$) is almost absolute acetic acid (99 per cent.), and becomes crystalline at a temperature somewhat below 15° C. (60° F.).

Acidum Aceticum (U. S. P., B. P.) contains 36 per cent. of absolute acetic acid U. S. P., 33 per cent. B. P.

Acidum Aceticum Dilutum contains 6 per cent. of absolute acetic acid U. S. P., 4.27 per cent. B. P. (Dilute acetic acid is used to form the official aceta except the Acetum Cantharidis, B. P.) 2–4 c.c. (½–1 fl. dr.).

[illegible]

Acetic acid is sometimes applied to the skin as a slight local irritant in contusions, and in very dilute solutions to cool the surface and to prevent excessive local perspiration. It has been used as a styptic in slight hæmorrhage, and may be inhaled for this purpose in epistaxis. Vinegar is also inhaled in cases of fainting, in order to induce a reflex stimulation of the vasomotor centre through irritation of the nostrils. In cases of poisoning with alkalies vinegar is often the most convenient acid and in addition is less likely to do harm than the inorganic acids.

Acetic acid itself is not used as a corrosive, but one of its derivatives, trichloracetic acid (CCl_3COOH), has been employed with good results.

Formic Acid resembles acetic acid in most points, except that it is more volatile and more irritant, that less of it is oxidized in the tissues, and that given in large quantities it is said to induce nephritis. It is quite useless in therapeutics.

The other acids of the acetic acid series resemble acetic acid in their effects, but become less irritant as they become more complex and less easily dissociated.

Lactic Acid resembles acetic acid in its behavior in the organism (see page 557). It was suggested at one time that sleep following muscular exertion was due to the lactic acid formed in the muscles, and this acid was therefore recommended as a hypnotic, but has been shown to be of no value for this purpose. Rickets, rheumatism and other diseases were also at one time attributed to the excessive formation of lactic acid in the tissues, but this

Oxalic (or acid K salt) for suicide. Resembles $MgSO_4$! Ca's for oxalate poisoning. Tartaric = gastritis 8 pts acid to 7 of $NaHCO_3$ for effervescence & pleasant acid taste. Not all combusted in tissues. Citric - all combusted. Lemonade; effervescent. Fresh lime juice in scurvy.

theory is only of historical interest. Under the impression that lactic acid was the normal acid of the gastric digestion, it was at one time used in dyspepsia.

Acidum Lacticum (U. S. P., B. P.) is obtained by the fermentation of milk sugar or grape sugar, and contains 75 per cent. of absolute lactic acid ($HC_3H_5O_3$). It is a colorless liquid of strong acid taste.

Lactic acid has been used recently as a caustic application to malignant ulcers and diphtheritic membranes.

Oxalic Acid is frequently used as a poison by suicides, either as such or as the acid potassium salt (salt of sorrel or essential salt of lemons). Poisoning has repeatedly occurred from oxalic acid having been mistaken for magnesium sulphate, which it resembles in appearance. The symptoms are those of acid poisoning, along with the specific effects of the oxalates (see page 560). Oxalic acid is not used in therapeutics.

Tartaric Acid induces symptoms of gastric irritation when taken in large doses, and has been the cause of fatal poisoning in a few cases. It is slowly absorbed, and some of it escapes combustion in the tissues and is excreted in the urine in the form of acid tartrate. (See Tartrates, page 542.)

Acidum Tartaricum (U. S. P., B. P.) ($H_2C_4H_4O_6$), colorless crystals very soluble in water. 0.3–1.3 G. (5–20 grs.). 0.3-1.3

Tartaric acid is prescribed with the carbonates and bicarbonates to form effervescent draughts; the tartaric acid ought to be slightly in excess in order to lend its pleasant acid taste, the usual proportion being about eight parts of acid to seven parts of sodium bicarbonate. These effervescent mixtures formed with the tartrates act as saline cathartics in large doses (see page 544). Tartaric acid may be prescribed in dilute solution with sugar and a drop of volatile oil as a lemonade, which is cheaper than that formed with citric acid.

Citric Acid resembles tartaric acid in its action, but appears less irritant, and no case of serious poisoning is recorded from its use. It is slowly absorbed like tartaric, but seems to be almost entirely oxidized in the tissues.

Acidum Citricum (U. S. P., B. P.) ($H_3C_6H_5O_7 + H_2O$) resembles tartaric acid in its properties for the most part. 0.3–1.3 G. (5–20 grs.). 0.3-1.3

Syrupus Acidi Citrici (U. S. P.) is ordinary syrup to which one per cent. of citric acid and spirit of lemon have been added, and is used only as a flavor. 1%

Citric acid and the citrates when added to drawn blood prevent clotting by combining with the calcium in a practically non-dissociating salt. When administered by the mouth it has no such effect on the circulating blood, and its use to lessen clot formation in the body is based on erroneous observation.

Citric acid is used to form lemonades and effervescent draughts. For lemonade 2–4 parts of citric acid may be dissolved in 1,000 parts of water, some sugar and a few drops of volatile oil being added. For effervescent solutions about 8 parts of the acid may be prescribed along with 7 parts of bicarbonate of soda, with directions to dissolve the two powders separately, mix the solutions and drink while effervescing. In large quantities this mixture acts as a saline cathartic; in smaller quantities it may be used to increase the alkalinity of the blood, and to render the urine less acid.

Lime juice and lemon juice, which contain considerable amounts of free citric acid, are generally preferred to the pure acid for lemonades to quench the thirst. Lime juice has been found of great benefit as a prophylactic in the treatment of scurvy, but this is not due to the citric acid, but to some unknown property of the fruit juices. Citric acid has been used in rheumatic affections, without any marked improvement being elicited, according to the best observers.

XX. CALCIUM.

The salts of lime are present in very large amount in the tissues of animals, and considerable interest attaches to their absorption, excre-

Most of inorganic material in bone & teeth. essential to all living matter. Salts insol so no salt action. Prec. colloids (eg proteins) – not redissolved in H_2O. The sol. lime salts [illegible] from stom. & int. with great difficulty; if weren't thrown down by alk. of intest would be cathartics. A little is absorbed, & circ. with protein, utilized by tissues or excreted, mostly by large intest.

tion and general action. They form the great mass of the inorganic constituents of the bones and teeth of the vertebrates and of the shells of the invertebrates. In addition it has been shown of recent years that they are present to a considerable amount in the soft tissues and are, in fact, essential to many forms of living matter, and to the activity of certain ferments.

Calcium and the other alkaline earths differ from the alkalies in possessing comparatively few very soluble salts, and they seldom effect such changes in the physical properties of the fluids of the body as have been described under salt-action and chloride of sodium. Even the soluble salts penetrate with greater difficulty into the various tissues of the body, which seem to have much less affinity for them than for the salts of the alkalies. They precipitate colloids, such as the proteins, in much more dilute solutions than the alkalies, and the precipitate is not redissolved by dilution with water.

Action.—The soluble lime salts are **Absorbed** with great difficulty from the stomach and intestine and retard considerably the absorption of fluid. They would presumably have a cathartic action were they not thrown out of solution very readily by the alkaline fluids. In addition calcium forms insoluble salts with all of the cathartic acid ions, so that no such double effect can be obtained as is seen from magnesium sulphate. (See Saline Cathartics, page 538.) The great proportion of the lime taken either in the food or as a remedy, unquestionably leaves the body in the stools entirely unabsorbed, while a small quantity of it is taken up from the alimentary canal whether the lime be administered in a soluble or in an insoluble form. This small quantity circulates in the blood, probably in combination with proteins, and is slowly excreted, unless there is a deficiency in the supply of lime, when it may be utilized by the tissues. When larger quantities are thrown into the blood by intravenous or hypodermic injection, the calcium of the blood remains abnormally high for some time, but all the calcium thus injected is not in the circulation throughout its stay in the body. Some of it is temporarily deposited in some unknown organ, and is gradually withdrawn and excreted after the first excess is eliminated.

The lime is **Excreted** in part in the urine, but for the most part through the epithelium of the large intestine. The administration of calcium increases the elimination of magnesium in the urine, and similarly magnesium absorbed leads to a larger excretion of calcium in the urine, while that in the fæces may be diminished. Abel and Muirhead have shown that some of the calcium ingested in the form of the hydrate is excreted in the urine as calcium carbamate ($Ca(CO_2NH_2)_2$) and probably other salts may be eliminated in part at any rate in this form. The carbamate is a very unstable salt, and breaks up in the urine, freeing carbonic acid and ammonia, while the calcium forms the carbonate of lime; the urine is often alkaline therefore and smells strongly of ammonia. Calcium lessens the phosphates of the urine, and therefore its acidity, by forming insoluble phos-

In bowel CaPO4 formed thereby decreasing phos absorption & urine's acidity
Constipation due to neuromusc effect or protective layer. Plenty of Ca in the
So does depend on anion. Intravenous = acceleration of heart then stoppage.
Even pin-point pupil. So therapeutically not used in excess in blood.
Ca starvation. Affects young. Rickets — osteomalacia N.S.

phates in the bowel, and thus preventing the absorption of the phosphates of the food. The small quantity of calcium absorbed from the alimentary canal has no very obvious effects; constipation is often induced by lime, but it is uncertain whether this arises from action on the bowel neuromuscular apparatus, or is the result of the insoluble calcium salts forming a protective covering over the epithelium and thus lessening the reflex peristalsis (compare tannin group). Except under special circumstances, the calcium of the food is always sufficient to supply the needs of the organism, so that lime salts given as remedies have after absorption no specific action due to the calcium, but owe their activity to the anion exclusively. Thus, calcium bromide may have some effect if absorbed, but this effect is due to the bromide ion, and would be the same if an equal proportion of sodium bromide were taken up by the blood. In the same way calcium hydrate when absorbed owes its activity to its alkalinity (hydroxyl ion) and not to the calcium, and apart from the method of its excretion, has the same effect in the tissues as an equivalent amount of sodium hydrate.

Soluble calcium salts injected directly into the blood vessels seem to be poisonous, their action resembling that of digitalis in some respects. They first accelerate and strengthen the heart, and in large quantities bring it to a standstill and also have a marked effect in contracting the vessels when perfused through them. In this way they may sometimes diminish the diuresis and glycosuria in animal experiments. Large quantities injected intravenously contract the pupil to pin-point size, apparently from action on the fibres of the sphincter muscle, for atropine has little effect on the myosis. Asphyxia causes dilatation after calcium, however, in the same way as in morphine poisoning. These effects are absent when the salts are taken up from the bowel, mainly no doubt owing to their slow absorption, partly perhaps to their forming albuminous compounds in their passage into the tissues.

Lime Starvation.—Excess of calcium in the organism is therefore little to be apprehended from the ordinary methods of administration, and lime salts are seldom used in therapeutics to induce changes in the organism through their presence in excess in the blood, like other remedies, such as morphine or strychnine. Another question arises, however, namely, whether the organism may not be rendered abnormal by a deficiency in the supply of lime, and whether this deficiency may be remedied by the administration of calcium salts.

The effects of a deficiency of lime in the food have been the subject of several very careful investigations, and while the adult animal does not seem to suffer greatly from a very considerable reduction of the calcium of the food, young growing animals have at the hands of some investigators developed marked abnormalities, resembling closely those observed in rickets and osteomalacia in the human subject. In lime starvation, as in rickets, there is a lessened deposit of lime in the bones, which retain their cartilaginous consistency and show other deviations from the normal condition; in rickets the bones alone are involved, while in animals deprived of calcium the soft tissues also show a lessened content of lime salts. Deficiency of the lime in the

Isolated organs grow better & live longer when Ca present in fluid.
Ca necessary for action of rennin on milk & for blood coag (in formation of
fibrin ferment (from prothrombin)). Lime salts by mouth do not accelerate blood clotting

food naturally affects young animals more than adults, because the former require much more calcium to build up the growing skeleton.

The effects of the withdrawal of lime have been studied in some **Isolated Organs.** Thus Ringer compared the behavior of the frog's heart when perfused with solutions of the salts of the alkalies with that of one perfused with the same solutions to which minute traces of lime were added, and found that the efficiency of the heart was much increased and that it survived very much longer under the latter conditions; Locke has recently shown that a similar relation exists between the mammalian heart and the inorganic elements of serum. Lime salts exercise a similar effect in voluntary muscle, which survives much longer when perfused with salt solution containing calcium than when sodium chloride solutions alone are used. Both the heart and skeletal muscle eventually cease to contract on electrical stimulation when perfused with physiological salt solution, but recover again when traces of lime salts are added to it. In the same way, the irritability of the frog's nerve persists much longer in salt solution containing a lime salt than in unmixed salt solution, and may be restored by the addition of lime, when it has disappeared after the prolonged action of the 0.6 per cent. chloride of sodium solution. Ciliated epithelium continues to wave rhythmically much longer in lime solution than in distilled water, in which it swells up and rapidly loses its activity. This probably explains the observation that some fish die very soon in distilled water but survive in water in which traces of lime are present. Lime is also necessary for the development of various ova; for instance, frog spawn kept in water devoid of lime salts fails to develop, or develops abnormally.

Lime salts are also indispensable in some processes which are not dependent on the presence of living cells. Thus rennet does not coagulate milk except when a lime salt is present, and the **Coagulation of the Blood** may be prevented by precipitating its calcium salts in the form of oxalates. Hammersten has recently shown that the lime salts are not necessary to the formation of fibrin, for this occurs in oxalate solutions if fibrin-ferment be added to fibrinogen. But the fibrin-ferment is not formed except in the presence of calcium salts, and when oxalates are added to the blood before this ferment is developed they prevent its formation and hinder clotting. When lime salts are added, the ferment is liberated and coagulation occurs at once. In other words, lime is not necessary for the activity of the fibrin-ferment, but for its development from the prothrombin or zymogen, in which it exists in the circulating blood. Lime salts taken by the mouth do not accelerate the clotting of blood.

Other ferments act in the absence of available lime salts. Thus pepsin digests when instead of hydrochloric, oxalic acid is added to it, but it is unknown whether pepsin is formed from pepsinogen in the absence of lime. The trypsinogen of the pancreas may be changed to trypsin by lime salts.

The higher organisms, both animals and plants, have thus been

Mg poisoning neutralized by injection of Ca

shown to require lime for some of their functions, and it is probably necessary for many others in which its importance has not yet been recognized. The lowest forms of life, however, including the bacteria and some of the moulds, seem to be able to live without it. In order to induce the effects of lime starvation, it is not always necessary to withdraw lime from the food, for they may be caused by the presence of any substance which prevents the dissociation of the calcium ion. Thus, oxalate solutions added to the blood or milk, or to the nutrient fluid for perfusion of the heart, have the same effects as the withdrawal of lime. Food containing large quantities of oxalate salts has in some cases induced symptoms in animals resembling those of lime starvation, and it seems possible that some of the symptoms of fluoride action are also explicable from their precipitating the lime salts of the food and of the blood.

by preven dissociati of Ca

In several instances a curious relationship has been shown to exist between the calcium and potassium salts. Thus when a frog's heart is perfused with sodium chloride solution containing a trace of calcium, the movements are not entirely normal, the contraction being somewhat prolonged and the relaxation much retarded. If a trace of potassium chloride is added, however, the contraction becomes normal in character. On the other hand the effect of potassium on the frog's heart is antagonized by the addition of lime. The same holds true for voluntary muscle, the salts of calcium tending to neutralize the effects of potassium, and *vice versa*, and in several other relations an antagonism has been observed between these two K^+Ca metals. Another marked antagonism has recently been studied by Meltzer, who shows that toxic quantities of magnesium can be completely neutralized by calcium. And, as the symptoms of magnesium poisoning in mammals are characteristic, the recovery of animals when calcium is injected is very striking; magnesium induces narcosis and anæsthesia, which is immediately counteracted by calcium, and the animal assumes its normal posture.

Another question that has excited much interest recently is the relation between sodium and calcium. It has already been noted that the frog's heart perfused with sodium chloride solution soon ceases to beat, but can be restored by the addition of calcium and potassium to the circulating medium. The ordinary explanation (Ringer, Howell) is that the calcium and potassium are necessary to the activity of the heart and that when pure salt solution is perfused these elements diffuse into it and are lost from the heart muscle; this diffusion is prevented if calcium and potassium be contained in the solution, and the heart, retaining the salts essential to its activity, continues to beat. Another explanation has been offered by Loeb, who supposes that the lime and potassium are not directly essential, but that they neutralize the poisonous effects of sodium. This poisonous action of sodium has not been generally recognized, but is well shown by the behavior of a small fish (fundulus) living in salt water, which can be transferred to distilled water without injury, thus showing that neither sodium nor calcium is necessary in its environment. But if it be put in sodium chloride solution of the same strength as sea water, it dies, so that sodium is poisonous to it unless when antagonized by the other constituents of sea water; the essential elements are calcium and potassium, for when these are added to the injurious sodium solution, the fish lives as well as in sea water. This series of experiments certainly forms a strong support for Loeb's theory that calcium is not directly essential to rhythmic movement, but only neutralizes the effects of sodium. On the other hand, the calcium salts themselves are poisonous when they are not counterbalanced by sodium and potassium; in this, as in many other

Alk. of Ca – lessen acidity. CaO = caustic. Anion acts. In rickets + osteomalacia due to failure of deposition of Ca present in food + body in abundance. However may be lime starvation

instances, there must be maintained between the inorganic constituents of the surrounding fluid an equilibrium, such as exists in sea water in the case of the fundulus, and in the blood plasma in the case of the heart and other organs.

The salts of the alkaline earths are said to inhibit the hæmolytic action of certain serums, while those of the alkalies have not this effect when applied in the same concentration; this may perhaps be connected with the tendency the former have to coagulate proteins. The formation of protein combinations is apparently the explanation of the disappearance of lime salts when they are perfused through organs or when pieces of tissue are soaked in them. Cartilage seems to combine more readily with lime than the other tissues.

Therapeutic Uses.—Calcium salts are used in medicine for a number of different purposes; thus the alkaline preparations may be prescribed to lessen the acidity of the stomach, and the oxide may be employed as a caustic. But these owe their use, not to the calcium ion, but to the other part of the molecule—the anion. As a matter of fact, calcium has few important effects of its own and is seldom prescribed for any action which it might have on the living tissues. The question has been raised, however, whether calcium may not be given therapeutically to supply a deficiency of lime in the body. The particular conditions which have been treated on this theory are rickets and osteomalacia, in both of which there is unquestionably too little lime in the bones, and the treatment has been thought to be rational, because symptoms similar to those of rickets have been induced in young animals whose food contained too small a proportion of lime. In the case of rickets and osteomalacia, however, there is no reason to suppose that the food is deficient in calcium; in fact, children are said to be more liable to rickets when fed on cows' milk than when nursed by the mother, although the milk of the cow contains more lime. On the other hand, patients suffering from rickets absorb lime and excrete it again in exactly the same way as normal persons, and although their bones contain unusually small amounts of lime, the other tissues contain rather more, or, at any rate, not less than normal. Rickets is not due to a lack of lime in the food, therefore, nor in fact in the tissues generally, but to some abnormal condition which prevents the lime salts from being deposited in the bones, although they are present in abundance in the blood. In cases of lime starvation similar symptoms may appear, but here the cause is the want of lime, which is not presented in sufficient quantities, although the bone-forming cells are ready to deposit it. In this case the other tissues are also deficient in calcium as well as the bones. From these considerations it follows that lime salts are not likely to be of benefit in rickets (and the same holds true for osteomalacia), unless when it is due to lime starvation, a condition which is unlikely to arise in the human subject. Experience has demonstrated also that the lime salts are quite incapable of improving either osteomalacia or rickets.

It has also been proposed to treat with lime cases in which the blood seemed less capable of clotting than normally—particularly hæmophilia, and the treatment has been extended to aneurism, hæmoptysis

Blood clotting (haemophilia etc) not augmented by Ca by mouth.
Parathyroid destroy lessens Ca in blood + brain = tetany. lime Ca.
Calx - unslaked lime $CaO + H_2O = Ca(OH)_2$ very weak so doesn't spread.
CaO a great organic disinfectant - cheap

and gastric and intestinal hæmorrhage. In hæmophilia there is no deficiency of lime in the blood, however, and still less is this the case in aneurism and hæmorrhage. And the administration of lime by the mouth does not accelerate or in any way alter the clotting of blood. Finally no distinct clinical results have been obtained by careful observers, and the treatment may be dismissed as erroneous. A still further development of the theory has led to the use of calcium in the most diverse conditions, in which it was suggested that the symptoms arose from excessive transudation of lymph into the tissues; and the clinical results are equally disappointing.

MacCallum has recently stated that in dogs from whom the parathyroid glands have been removed, the lime content of the brain and blood may be very much diminished, and that the symptoms of tetany which arise after the operation may be relieved by lime salts given intravenously or by the mouth. A few cases of tetany in man also improved under treatment with calcium salts.

Another treatment of aneurism and hæmorrhage of recent introduction is by **Gelatine**, administered by the mouth or hypodermically (100 c.c. of a 1–5 per cent. solution). This is based on a series of experiments which seemed to indicate that the coagulation of the blood is hastened by gelatine, but which have not been confirmed by later investigators. Aneurism of the aorta, hæmoptysis, gastric, intestinal, renal and uterine bleeding have all been treated with gelatine with no benefit. In some cases gelatine has proved the channel of infection by tetanus.

PREPARATIONS.

✓*Calcii Chloridum* (U. S. P., B. P.) ($CaCl_2$), a white salt with a sharp, saline taste, very deliquescent and soluble in water. 0.3–1 G. (5–15 grs.). 0.3-1 G

Calcium chloride is the salt which gives the least complicated calcium action, and is consequently seldom used, because, as has been explained, the calcium ion is of comparatively little service in therapeutics. It has a strong attraction for water and is therefore more irritant than the other chlorides of the alkalies and alkaline earths, and ought to be prescribed only in dilute solution. It is absorbed with great difficulty, and has been suggested in the treatment of some forms of dyspepsia and in hæmorrhage. Instead of the chloride, the lactate has been employed in the same doses.

Calx (U. S. P., B. P.) (CaO), unslaked lime, is a corrosive and disinfectant, and is changed at once to the hydrate in the presence of water. It differs from the caustic alkalies in the insolubility of its hydrate, which therefore fails to penetrate deeply and does not spread so widely as potassium and sodium hydrates. It is seldom employed alone as a corrosive, but mixed with potassium hydrate as Vienna paste (*Potassa cum Calce*, U. S. P.) has had some popularity.

It is used as a disinfectant where large quantities of organic matter have to be rendered harmless, as in epidemics, on battle fields and in the dejections of large hospitals. It ought to be mixed with the matter to be disinfected as thoroughly as possible. Lime possesses the advantage over other disinfectants of being cheap and easily procurable in large quantities.

Calcii Hydras (B. P.), slaked lime ($Ca(HO)_2$), may also be used as a disinfectant.

LIQUOR CALCIS (U. S. P., B. P.), lime water, is a saturated solution of calcium hydrate or slaked lime and contains about 0.15 G. in 100 c.c. (½ gr. in 1 oz. B. P.). It is a clear fluid with a saline and feebly caustic taste. 30–100 c.c. (1–4 fl. oz.). 30-100 cc oxide & OH caustic, alk (neut. gastric juice) ppt proteins = astringent in intest (surface [illegible]) lime water in vomiting dyspepsia, in typhoid & intest irrit as subdivides milk. The syr in oxalic acid poisoning.

✓ **Syrupus Calcis** (U. S. P.), **Liquor Calcis Saccharatus** (B. P.), syrup of lime, contains calcium hydrate kept in solution in water by sugar, with which it is probably combined chemically. The amount of lime contained varies greatly, but is much larger than in lime water. The B. P. preparation is said to contain nearly 2 per cent. by weight, or 8 grs. to the oz. 1–4 c.c. (15–60 mins.). 1-4 cc

✓ **Linimentum Calcis** (U. S. P., B. P.), lime liniment, or Carron oil, contains equal parts of lime water and olive or linseed oil. Burns

The preparations of the oxide and hydrate owe their activity chiefly to their alkalinity and not to the calcium, but differ from the hydrates of the alkalies in their insolubility and in their slow absorption. Lime water and the syrup are slightly caustic, more especially the latter and tend to neutralize the gastric juice. They have an astringent effect in the intestine which has not yet been explained, but is probably due to their forming an insoluble compound with the surface proteins, in the same way as tannic acid, or to their being deposited as the carbonate or phosphate and thus protecting the epithelium from irritation. Lime water is used in some dyspeptic conditions, especially in vomiting. It is often added to milk in intestinal irritation in children and in typhoid fever, as it is found that milk thus treated coagulates in finer particles than when given alone, and is better digested and less liable to disturb the intestine. Lime water or syrup of lime is also used as an intestinal astringent in diarrhœa, especially in children. As an antacid in the stomach, lime is inferior to magnesia and other alkalies, because it tends to delay the evacuation of the contents. Lime water has been used in rickets, which seems singularly irrational, for cows' milk contains a somewhat higher percentage of lime. It has also been sprayed against the false membrane of diphtheria, which it is said to dissolve. Lime water is not applicable in cases of acid poisoning, as it contains much too little of the base to be serviceable, but the syrup may be used, or lime shaken up with water (milk of lime). The treatment with lime is specially indicated in cases of oxalate poisoning.

Lime water has been used externally as a protective, mildly astringent application to ulcers, and the lime liniment has been largely used in the treatment of burns. It derives its name of Carron oil from having been used for this purpose in the iron works at Carron.

1-4 g ✓ *Calcii Carbonas Præcipitatus* (U. S. P., B. P.), precipitated chalk ($CaCO_3$). 1–4 G. (15–60 grs.).

1-4 g ✓ *Creta Præparata* (U. S. P., B. P.), prepared chalk, chalk purified by washing and suspension in water ($CaCO_3$). 1–4 G. (15–60 grs.).

2 g ✓ **Pulvis Cretæ Compositus** (U. S. P.), a mixture of prepared chalk, sugar and acacia. 2 G. (30 grs.).

Pulvis Cretæ Aromaticus (B. P.), aromatic chalk powder, contains chalk along with sugar and a number of carminatives belonging to the group of volatile oils. 10–60 grs.

Pulvis Cretæ Aromaticus Cum Opio (B. P.) is a mixture of 39 parts of the aromatic powder with one of opium, and therefore contains 2½ per cent. of opium. 10–40 grs.

16 cc. ✓ **Mistura Cretæ** (U. S. P.), chalk mixture, is chalk suspended in water by means of gums. 16 c.c. (½ fl. oz.).

mistura
$CaCO_3$ in hyperacidity with diarrhoea. Astringent for ulcers (as powder)
$CaCO_3$ chief constituent of tooth powders.

The preparations of the carbonate of lime are used as antacids in hyperacidity of the stomach, especially when this is combined with a tendency to diarrhœa. The mixture or the aromatic powder B. P., is the form generally used, and may be prescribed with opium or with other astringents. Chalk has also been used in rickets.

Externally, prepared chalk is used as a powder to protect irritated parts of the skin and occasionally in ulceration; it is the chief ingredient in most tooth powders. In older treatises on therapeutics great virtues are ascribed to various natural objects which are composed for the main part of chalk or other salts of lime, and among which burned bones, coral, coralline and cuttlefish bone may be mentioned.

Calcii Phosphas Præcipitatus (U. S. P.), *Calcii Phosphas* (B. P.) ($Ca_3(PO_4)_2$), a white insoluble powder. 0.3–1 G. (5–15 grs.).

Syrupus Calcii Lactophosphatis (U. S. P., B. P.), a preparation in which a soluble double salt of lime is contained in solution. 4–8 c.c. (1–2 fl. drs.).

A glycerophosphate of calcium has also been advised recently. These phosphate preparations have been used in rickets and osteomalacia, and in phthisis and other tubercular diseases, but the best authorities are agreed that lime salts are of no value in rickets and osteomalacia (see page 576), and experience with them in tubercular conditions is not more encouraging.

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XXI. BARIUM AND STRONTIUM.

Barium is the most poisonous of the three common alkaline earths, but resembles the others in penetrating with difficulty into the epithelium of the alimentary canal, and is therefore absorbed very slowly. It has a characteristic action on many forms of muscular tissue, resembling closely that of veratrine, and the contraction of the frog's muscle under barium is thus stronger than normally, and is very greatly prolonged; this action is not opposed by curara and is therefore believed to be exerted on the contractile substance directly. The frog's heart beats more strongly, but more slowly from a similar action on the muscle fibres, and the walls of the stomach and intestine are thrown into violent contraction from the action of the metal on the unstriated muscle fibre. There is some question as to whether the central nervous system is acted on in the frog, but in the mammal barium salts injected intravenously cause violent tonic and clonic spasms, from their stimulating the spinal cord and medulla oblongata. The action on the alimentary canal induces vomiting and purging with very active peristalsis. The heart is accelerated and the blood-pressure is enormously increased at first, and then undergoes slow undulations for some time. The increased tension may be due to the cardiac action in part, but is chiefly to be ascribed to a very marked contraction of the muscular walls of the vessels. The frog's heart eventually assumes an irregular peristaltic form of contraction and ceases in systole, as in digitalis poisoning, and the changes in the mammalian heart also resemble those caused by this series. Barium in sufficient quantities finally paralyzes the central nervous system. In fatal poisoning in animals hæmorrhages have been found in the stomach, intestine, kidney and other organs.

Barium is quite incapable of replacing calcium in its relations to living matter, and accordingly chloride of sodium solutions to which barium chloride has been added do not tend to keep the frog's heart active as do those containing lime. Some authors hold that barium can replace calcium to an imperfect degree in the coagulation of the blood, but this is denied by others. Potassium salts tend to neutralize the effect of barium on the heart and muscles, the relation resembling that which they bear to lime.

Barium is absorbed slowly from the intestine and is found to be stored in the bones to some extent, and to be excreted by the intestinal epithelium, only traces appearing in the urine.

It has been suggested as a substitute for digitalis, but has seldom been used in practical therapeutics. In veterinary practice it is often employed as a purgative. Crawford states that the loco-weed poisoning met with in the western states is due to the cattle feeding on plants containing barium.

Strontium is a comparatively inert substance even when injected directly into the blood, resembling calcium in its action in the body as far as is known, but being even less poisonous. It contracts the muscles somewhat, tends to lessen the dilatation of the heart, and prolongs the contraction of muscle, though only to a slight extent. It has not the antagonistic effects to magnesium which are possessed by calcium, nor, on the other hand, does the last named prevent the symptoms induced by large quantities of strontium. It is absorbed very slowly from the intestine like the other alkaline earths, and is deposited in small quantities in the bones of growing animals, especially when there is a deficiency of lime in the food; but it cannot be used to replace the calcium of the food, animals treated thus showing the symptoms of lime starvation. It is excreted in small quantities by the urine, but mainly by the bowel. Strontium salts have been used to a limited extent in therapeutics, not for the effect of the strontium ion, but for the bromide, iodide or salicylate effects of its salts. In view of the fact that the strontium salts are more slowly absorbed than the coresponding ones of sodium and potassium, there would seem to be good grounds for abandoning their use.

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Inert S in ali canal → sulphides & hydrosulphuric acid (poison)
Sulphides irritant to bowel = peristalsis & purgation. weak salts +
Carbonic acid → hydrosulphuric acid. By hypo = violent convuls

XXII. SULPHIDES AND SULPHUR.

The ordinary sulphides of the alkalies are of little importance in themselves, as they are seldom used in therapeutics. The effect of hydrosulphuric acid, however, apart from its local irritant action, is due to the sulphide which it forms in the blood, and the study of this powerful poison therefore involves a preliminary examination of the effects of the sulphides. Again, sulphur is in itself inert, but is changed to sulphides and hydrosulphuric acid in the alimentary canal, and the effects induced by its administration are due to these bodies, and not to the original element.

Action.—The sulphides are very weak salts, for even carbonic acid is capable of liberating hydrosulphuric acid, and wherever they come in contact with it in quantity, there is a tendency to form free acid, which acts as a powerful local irritant; it is not impossible that the sulphides have an irritant effect of themselves in addition to that of the hydrosulphuric acid. The sulphides accordingly act as irritants in the stomach and bowel, and in the latter induce increased peristalsis and purgation. When injected subcutaneously in the frog, sodium sulphide causes a narcotic condition from depression of the central nervous system, and in sufficient quantities weakens the skeletal muscle and the heart, which continues to beat after complete paralysis has been obtained, but eventually ceases in diastole. Harnack has recently shown that after the narcosis has lasted for some time, a new condition follows, if only small quantities have been given, and especially if the frog is healthy and is kept cool. This consists in an enormous increase in the reflex irritability, which induces convulsions resembling those of strychnine poisoning in their general character, but differing from them in lasting continuously for weeks or even months at a time. The animal lies in an extended and tense condition throughout, and passes into complete opisthotonos on being touched.

Sulphides injected intravenously in mammals induce violent convulsions, which seem to be of cerebral origin, for they do not occur in the hind limbs when the spinal cord is cut. The respiration is at first accelerated and later dyspnœic and finally ceases, this, along with the paralysis of the vasomotor centre, being the cause of death. The heart does not seem to be seriously affected except indirectly through the failure of the respiration and the fall of the blood-pressure.

Sulphide solutions added to drawn blood reduce the oxyhæmoglobin at once, and give the blood a dark venous color. At the same time a compound of sulphide and hæmoglobin is formed, the chemistry of which is still very obscure, but which would seem to be more nearly related to methæmoglobin than to hæmoglobin. It is known as sulpho-hæmoglobin or as sulpho-methæmoglobin, and gives the blood a greenish color when a thin layer is examined, while a thicker layer is dark red-brown. This sulpho-hæmoglobin possesses a characteristic spectrum, marked by a dark line in the red to the left of the D line. Larger quantities give an olive-green color to the blood, and the spectrum of sulpho-hæmoglobin disappears. When sulphides are injected into frogs, and more especially when sulphuretted hydrogen is inhaled, the blood gives the characteristic spectrum during life, but this does not seem to be the case in mammals, although sulpho-hæmoglobin is formed soon after death. The blood changes are not the cause of death in poisoning, as was formerly supposed, but the direct action of the sulphides on the central nervous system.

Sulphides absorbed into the blood are rapidly oxidized, and are excreted in the urine in the form of sulphates and of organic sulphur compounds of unknown constitution. Small quantities escape by the lungs, and give the breath the disagreeable odor of sulphuretted hydrogen, and according to some authorities, some is excreted in this form in the perspiration.

The sulphides dissolve the horny epidermis and hair very readily when they are applied to the skin. If the application is continued, some irritation and redness is produced.

Hydrosulphuric Acid (sulphuretted hydrogen, hydrogen sulphide (H_2S)) differs from the sulphides in being a gas, and in its strong irritant properties, which it shares with other acids (see page 562). It has not infrequently given rise to poisoning, as it is formed in large quantities in the course of the putrefaction of sulphur compounds, such as proteins. Sewer gas often contains it in quantity, and workmen employed in cleansing sewers or cesspools have often suffered from its effects. When inhaled in concentrated form it is almost immediately fatal, the patient losing consciousness at once, and the respiration ceasing after a few seconds. In smaller quantities it causes immediate unconsciousness, lasting for several hours and then passing into fatal coma, which is often interrupted by violent convulsions. In both of these forms the symptoms are due to the direct action of the sulphides on the brain and medulla oblongata. Persons exposed to a very dilute vapor of sulphuretted hydrogen suffer from local irritation of the eyes, nose and throat, indicated by pain and congestion of the conjunctiva, sneezing, dryness and soreness of the mouth and throat, and a reflex increase in the secretion of tears, saliva and mucus. Headache, dulness, giddiness and loss of energy are complained of; the symptoms frequently appear only some time after the exposure to the poison. According to Lehmann, death in animals exposed to these dilute fumes is due in part to œdema of the lungs caused by the local irritant action. He found that one part of hydrosulphuric acid in 5,000 of air was sufficient to induce symptoms in man, and that an atmosphere containing one part in 2,000 could be respired for only a short time, and gave rise to alarming symptoms; he supposes that about one part of hydrosulphuric acid in 1,000 parts of air is sufficient to poison man fatally in a very short time.

The poisonous effect of sulphuretted hydrogen is due in part to its local irritant action, in part to its directly affecting the central nervous system. The changes in the blood occur during life only after very concentrated gas is inhaled, although they may indicate the poison after death from more dilute vapor, for the tissues in general tend to assume a green color sooner after hydrosulphuric acid poisoning than in the course of ordinary putrefaction.

Hydrogen sulphide is destructive to most forms of life, even when present in comparatively small amount. Even the microbes of putrefaction, which produce it themselves, are eventually killed by this gas, unless it escapes freely.

PREPARATIONS.

Potassa Sulphurata (B. P.), liver of sulphur (Hepar Sulphuris), is a mixture of polysulphides and thiosulphides, often containing sulphate of potassium. The greater part is formed of potassium trisulphide (K_2S_3) and of potassium thiosulphate ($K_2S_2O_3$). It is soluble in water and possesses an unpleasant saline taste, and an odor of hydrogen sulphide, which is formed by its decomposition in water.

Calx Sulphurata (U. S. P., B. P.), sulphurated lime, is another impure preparation containing at least 60 per cent. of calcium monosulphide (CaS) (50 per cent. B. P.), with some calcium sulphate and charcoal. It forms a grayish powder, insoluble in water, and gives off hydrogen sulphide. 0.015–0.06 G. (¼–1 gr.).

These preparations are seldom used internally, and, in fact, the sulphurated potassium has been found to be a dangerous poison, from the hydrogen sulphide given off by it in the bowel acting both locally and after absorption.

Sulphurated lime renders hair + horny excrescences soft + gelatinous for removal. Most S out as S. Also as urine ~~and [illegible]~~ as sulphates. Sulphides -> H_2S - eructation + odor to breath.

Sulphur Praecipitatum (Milk) S/ a good aperient

Sulphurated potassium is used to a very limited extent as an external application in certain skin diseases, particularly in acne, and to destroy skin parasites, such as that of scabies. It is used as an ointment (1 part to 10 parts), and is somewhat irritant.

Sulphurated lime is used occasionally to remove hair and horny excrescences, both of which it renders soft and gelatinous, but its frequent use is liable to cause irritation.

Many mineral springs contain hydrogen sulphide in small amount, and these have obtained wide celebrity in the treatment of various chronic respiratory and skin diseases and in syphilis, gout, rheumatism and chronic metallic poisoning (lead, mercury). Most of these springs are hot, and it is open to question whether the small amount of the gas contained in the water is of any efficacy, and whether the heat of the water and the hygienic conditions are not the true cause of the improvement observed in these cases. Sulphur baths are also formed artificially by the addition of sulphurated potassium (2–8 oz.) to an ordinary hot bath; a small quantity of acid is sometimes added, in order to free the hydrogen sulphide more rapidly.

Sulphur is in itself an inert body, but while much the greater portion escapes in the stools unchanged when it is swallowed, some of it forms sulphides in the mucous membrane of the intestine, and these cause irritation, increased peristalsis and mild purgation; in large quantities it has caused, in some instances, more severe symptoms with bloody evacuations. The sulphides form some hydrogen sulphide, which gives rise to eructation. Some 10–20 per cent. of the sulphur taken by the mouth is absorbed as sulphide, which is excreted to a small extent by the lungs, giving the characteristic disagreeable odor to the breath, and to a much larger extent by the urine as sulphates and in organic combination. In one experiment, Presch found the urea of the urine considerably increased (10 per cent.) under sulphur, and Umbach found it increased by pure calcium sulphide; whether, as this would suggest, the sulphides augment the nitrogenous waste as a general rule, can only be determined by further experiment.

Applied to the skin in ointment, sulphur appears to be formed in part to sulphide, particularly if some alkali be added.

PREPARATIONS.

Sulphur Sublimatum (U. S. P., B. P.), Flowers of Sulphur, sublimed sulphur.

Sulphur Lotum (U. S. P.), washed Flowers of Sulphur, is prepared by washing the sublimed sulphur with water and ammonia. These preparations form fine yellow powders insoluble in water and very slightly soluble in alcohol. 4 G. (60 grs.) in powder or sometimes in tablets. 4 G

Sulphur Præcipitatum (U. S. P., B. P.), Milk of Sulphur, is prepared from ~~sulphide of calcium~~ by precipitation and forms a fine, almost white powder without odor or taste, insoluble in water, and only very slightly soluble in alcohol. 1–4 G. (15–60 grs.). 1-4 G

Unguentum Sulphuris (U. S. P., B. P.), formed from sublimed sulphur, which is also contained in the Compound Liquorice Powder.

Trochiscus Sulphuris (B. P.) contains 5 grs. of sulphur.

Confectio Sulphuris (B. P.), 60–120 grs.

Crude sublimed sulphur often contains arsenic and other impurities, and ought not to be used in therapeutics. The milk of sulphur is in a finer state of division than the flowers, and is said to be a somewhat more active aperient.

Aperients - sulfides formed - irritant - soft formed stool - [illegible] [illegible] hemorrhoids. Most of S eliminated in urine as sulphates & organic [illegible]

Sulphur is used as an aperient powder, and may be added to rhubarb or magnesia for this purpose; it causes a soft, formed stool, and seldom induces more than one evacuation. It is prescribed for children, and in cases of hæmorrhoids, in which it is often very beneficial, not owing to any specific effect on the hæmorrhoids, but because it renders the stool softer and less liable to cause irritation mechanically.

Sulphur has been advised in a variety of constitutional diseases and in chlorosis, skin and joint affections, but it is impossible to state at present whether it has any effect in these apart from its improving the condition of the intestine.

Sulphur ointment has been used in some skin diseases, particularly in scabies, but has been supplanted to a large extent by the balsam of Peru. It has been applied in powder to diphtheritic membranes.

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XXIII. CHARCOAL.

Charcoal, like spongy platinum and other porous bodies, possesses the property of accumulating gases in its interstices and thus ordinarily contains considerable quantities of oxygen. When brought into contact with decomposing matter, the oxygen is released and hastens the oxidation of the putrefying mass, while the gases arising from the bacterial action are absorbed by the charcoal, which thus acts as a deodorant. It has no direct action on the microbes of putrefaction, but may by introducing oxygen favor the development of the aërobic organisms at the expense of the anaërobic. Besides gases, charcoal also absorbs many colloid bodies, such as the coloring matter of plants and proteins.

Animal charcoal appears to possess no advantages over wood charcoal, and they both act when moist almost as efficiently as in the dry state.

Charcoal has no appreciable effect on the economy, apart from its lessening the eructations of gas and the flatulence in some cases. It passes through the stomach and intestine unabsorbed, and may in rare cases cause some mechanical irritation and increased movement. Charcoal given in a state of suspension to animals is said to have been found in the epithelial cells of the intestine and even in the blood vessels, but does not have any effect attributable to its absorption in man. (*Wild.* Med. Chronicle, 1896.)

PREPARATIONS.

Carbo Animalis (U. S. P.), animal charcoal, bone-black, prepared from bone.

Carbo Animalis Purificatus (U. S. P.) is prepared by boiling bone-black with hydrochloric acid in order to remove the lime and other impurities.

Carbo Ligni (U. S. P., B. P.).—Charcoal prepared from soft wood and finely powdered.

Charcoal is used internally to remove the gases in flatulence and dyspepsia, and is prescribed in powder or in the form of charcoal lozenges. It may be given in any quantity, but is most commonly prescribed in 4–8 G. (60–120 grs.) doses. It is employed externally as a deodorant in cases of foul ulcers, cancerous sores, or malodorous secretions from any source; for this purpose it is added to poultices or used dry in bags of fine cloth.

XXIV. BORACIC ACID AND BORAX.

Boracic or boric acid ($B(OH)_3$) is a very weak acid, and it is doubtful whether the hydrogen ions or acidity play any part in its action, or whether the whole is not to be referred to the rest of the molecule. The ordinary sodium compound, borax, $Na_2B_4O_7$, is stated by some authors to be equally active, but is alkaline in reaction, so that the exact relative importance of the two ions of boric acid cannot be determined.

Action.—Boracic acid and borax are only feebly toxic, but large quantities taken by the mouth cause gastric and intestinal irritation, as is evidenced by vomiting and purging, and even smaller amounts are said to act as mild aperients in some cases. Not infrequently repeated small doses of boric acid have induced albuminuria, especially in persons predisposed to it. Moderate doses are without effect on the metabolism, but larger quantities (5–10 G. per day in dogs) increase the nitrogen excretion in the urine. A dose of 30–60 grs. of boric acid is found to increase the bulk of the fæces in man by retarding the absorption of the proteins and fats.[1] Both borax and boracic acid are rapidly absorbed by the bowel, and do not affect the intestinal putrefaction.

Boracic acid has been widely used as an antiseptic dressing, and a number of cases of serious poisoning have been recorded from its absorption. The symptoms arose in part from the alimentary canal, uneasiness in the abdomen, vomiting, diarrhœa, dryness of the throat and difficulty in swallowing; sleeplessness, great muscular weakness and depression, dimness of sight and headache were also complained of, and in severe cases collapse and death followed. The prolonged use of boracic acid, internally or externally, has repeatedly led to falling of the hair, eczema and psoriasis. Papular eruptions and local œdemas and swelling of the skin appear, and a gray line on the gums, similar to that seen in lead poisoning, is stated to occur along with irritation of the mouth. These skin affections appear also when borax is used in large quantities as an antiseptic dressing.

Boracic acid and borax are excreted in the urine, in which they appear within a few minutes after ingestion; over half the quantity taken is excreted within 12 hours, but afterward the elimination proceeds more slowly, so that traces may be found in the urine for 5 days or more. It is sometimes stated that the urine is increased by borax, but this is not borne out by experiment, and Chittenden and Gies found it actually diminished in amount; the reaction becomes alkaline after sufficient amounts of borax, as after any other alkaline preparation. Boracic acid and borax have some antiseptic power, for in 2½ per cent. solution almost all forms of bacilli stop growing; but they are not destroyed, even the delicate anthrax bacilli being found capable of further growth after exposure to a 4 per cent. solution for 24 hours. Boracic acid is therefore valueless as a disinfectant, but has been used as an antiseptic dressing; it has the advantage over many other antiseptics of inducing very little irritation and of being only slightly poisonous, but experience has shown that it cannot be used with impunity in very large quantities.

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[1] The body weight often falls under borax treatment, and this has been attributed to augmented fat destruction by Rost and Rubner, who state that a corresponding increase in the carbonic acid elimination accompanies it.

PREPARATIONS.

Acidum Boricum (U. S. P., B. P.), Boric or Boracic Acid (H_3BO_3), colorless crystals, with a faintly bitter taste, soluble to about four per cent. in water, more so in alcohol and glycerin. 0.3–1 G. (5–15 grs.).

Glyceritum Boroglycerini (U. S. P.), *Glycerinum Acidi Borici* (B. P.). Boroglycerin is a compound formed by heating boric acid in glycerin, and the official glyceritum or glycerinum contains this dissolved in glycerin, about 31 parts of boric acid being used to form 100 parts.

Liquor Antisepticus (U. S. P.), containing 2 per cent. of boric acid, along with benzoic acid, thymol, eucalyptol and oils of peppermint, wintergreen and thyme.

Unguentum Acidi Borici (B. P., U. S. P.), 10 per cent.

Sodii Boras (U. S. P.), *Borax* (B. P.), Borax ($Na_2B_4O_7 + 10H_2O$) forms colorless crystals with a sweetish alkaline taste. It is soluble in water (16 parts) to which it gives an alkaline reaction. 0.3–1.3 G. (5–20 grs.).

Glycerinum Boracis (B. P.) (1 in 6).

Mel Boracis (B. P.).

Boracic acid has been used as a surgical antiseptic in solution (four per cent.), ointment, or lint, and the solution of the acid or of borax is also used as a wash in aphthæ and other forms of irritation of the mouth. Boracic acid solution has been given internally in dilute watery solution as a genito-urinary disinfectant, has also been injected into the bladder, and is frequently used in ophthalmic surgery, as being less irritant to the eye than the more powerful antiseptics. In internal medicine the acid and the salt have been used in epilepsy, and also in the hope of dissolving uric acid calculi, but have not been shown to be efficient for either purpose. Boracic acid and borax are sometimes added to milk or other food as preservatives, and it has been much discussed whether the habitual use of such preserved foods is likely to prove deleterious to the health. The general result of the investigations is that, while no preservative should be added to food unless it is absolutely unavoidable, boric acid is less liable to derange the health than most other preservatives. Foods preserved with boracic acid should not be used by delicate individuals or by children, however, and the quantity of the acid used must be strictly limited.

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XXV. CARBONIC ACID.

Carbonic acid is contained in considerable quantity in many therapeutic preparations, notably in the effervescent cathartics and antacids, and also in many beverages, such as soda water, potash water, champagne and other sparkling wines. In some of these it is formed by the action of an acid such as citric or tartaric acid on carbonates, in others it is liberated in the course of fermentation, while in the artificial aërated waters it is forced into solution under high pressure. The last are therefore simple solutions of carbonic acid, while in the others more powerful agencies—cathartic salts or alcohol—are contained in addition.

Carbonic acid has a weak irritating action when applied in quantity; thus in baths charged with carbonic acid, a slight reddening of the skin has been observed, and some irritation and prickling of denuded surfaces is produced; a stream of carbonic acid directed against a wound or burn causes considerable heat and pain. Pure carbonic acid gas causes spasm of the glottis when inhaled, and even when it is much diluted, some irritation in the respiratory passages may follow at first. Solutions of carbonic acid induce reddening of the mucous membrane of the mouth and stomach, and are very rapidly absorbed, owing to the congestion and increased blood flow in the stomach wall which follows their administration. Much of the carbonic acid is thrown up by eructation, but some of it is absorbed and is excreted by the lungs. The absorbed acid has no effect on the organism, but the slight irritation of the stomach may cause increased appetite and a feeling of well-being. The rapid absorption of the water in which it is dissolved is followed by an augmented secretion of urine, and the carbonic acid waters are therefore used in preference to ordinary waters where a rapid flushing of the tissues and a profuse secretion of urine is desired. In addition, the slight irritation of the mouth and stomach renders them more acceptable than ordinary waters in fever and in other diseases accompanied by intense thirst; a mixture of milk and aërated water is often very grateful. The presence of carbonic acid in the sparkling wines leads to the rapid absorption of the alcohol also, and this action on the stomach may explain their being more exhilarating than other wines containing an equal amount of alcohol. The slight irritant effect of carbonic acid in the stomach has proved of benefit in some forms of gastric catarrh, such as that following alcoholic excess. Carbonic acid waters are also useful in the vomiting of pregnancy and in seasickness.

The prolonged application of carbonic acid to the mucous membranes leads to local anæsthesia, and numbing of the skin is also stated to occur under similar treatment.

Carbonic acid is absorbed from all the mucous membranes, from the skin and from the lungs. The gas has no effect after absorption except when inhaled, however, as when absorbed in any other way it is at once excreted by the lungs, and the amount absorbed never alters appreciably the normal percentage of carbonic acid in the blood.

When carbonic acid is inhaled unmixed with oxygen, it induces asphyxia, partly from a specific action which it exerts on the central nervous system, but chiefly from the absence of oxygen. Its effects are, therefore, very similar to those of any indifferent gas, such as hydrogen or nitrogen, and the symptoms are those of ordinary asphyxia. When, however, carbonic acid is inhaled mixed with a sufficient amount of oxygen, the specific effects of the gas are observed without any asphyxia. The symptoms are those of transient stimulation and subsequent depression of the central nervous system and heart. The first stage is marked by a very short period of psychical exaltation, with deep respirations, a slight rise in the blood-pressure and a moderately slow pulse. Very soon, however, unconsciousness, loss of the spontaneous movements, and later of the spinal reflexes follow, the respiration becomes somewhat slower and shallower, the pulse continues slow and the heart is weaker. If the inhalation be continued the respiration fails, the heart continuing to beat for a short time, though weakly. The symptoms of the first stage seem to be due to a direct stimulant action on the cerebrum and on the vagus, vasomotor and respiratory centres, while the second stage resembles that induced by the ordinary anæsthetics, and is evidently caused by depression of the central nervous system and of the heart muscle. In fact a mixture of carbonic acid and air has been used as an anæsthetic in one or two surgical operations. Death from carbonic acid poisoning is not preceded by convulsions, those observed in ordinary asphyxia being due to the absence of oxygen, and not to the excess of carbonic acid; it is still undecided by which of these factors the increased peristalsis seen in suffocation is caused. In well diluted vapor the symptoms of exaltation alone are observed, no anæsthesia following. A mixture of 5 per cent. carbonic acid in air causes acceleration and deepening of the respiration without further changes.

Carbonic acid in excess acts as a poison to other organs besides the central nervous system and the heart, although this effect is not seen in mammals. Frog's muscle loses its irritability rapidly, the ciliated epithelium ceases movement and the motor nerves, after a short period of increased excitability, are paralyzed by exposure to an atmosphere of carbonic acid. The blood assumes the venous color when shaken with the gas, and prolonged contact produces acid hæmatin, as does any other acid. It is a general poison to the protoplasm in mammals, apart from the effects on the central nervous system, for the combustion in the tissues is lessened to an extraordinary degree, as is evidenced by the very small amount of oxygen absorbed.

Carbonic acid is the natural stimulus of the respiratory centre, and it has been suggested that some forms of dyspnœa might be treated by the inhalation of carbonic acid diluted with air; the carbonic acid absorbed from the lungs would then strengthen the action of that already present in the blood on the flagging centre.

Mineral waters containing large quantities of carbonic acid in solution are often recommended as baths in various chronic diseases, such as rheumatism.

The effects may be due to the carbonic acid in part, but these waters also contain salts in solution.

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XXVI. CHLORINE AND BROMINE.

Chlorine and bromine resemble each other closely in the effects which they induce in all forms of living matter. These may be explained in part by their replacing hydrogen in its combinations in the proteins and forming hydrochloric or hydrobromic acid with the hydrogen set free, in part by their combining with the hydrogen of water and thus liberating nascent oxygen, which then acts on the tissues. These processes are believed to account for the fact that chlorine is a much more powerful disinfectant in moist air than in dry. In the higher organisms all of these reactions probably occur together.

Action.—Chlorine and bromine are general protoplasm poisons; thus 3 parts of chlorine in 1,000 parts of moist air are sufficient to destroy the spores of most bacteria in the course of three hours, and the infusoria and the higher plants have been shown to be equally susceptible to the influence of the gas. Even smaller quantities of bromine are disinfectant.

In the higher animals and in man chlorine and bromine act as irritants. Thus chlorine water (a saturated solution of chlorine in water) induces irritation and redness of the skin, and even blistering, when the gas is prevented from escaping. Bromine also causes very painful blistering, the fumes penetrating more deeply into the tissues than the non-volatile irritants, and causing more widespread irritation. Bromine or chlorine water, when swallowed, elicits intense inflammation and corrosion of the mouth, throat, and stomach, with collapse and all the ordinary effects of gastric irritation. Air containing even a very small proportion of chlorine irritates the eyes, nose, larynx and the deeper respiratory passages, the bronchi and lungs seeming more susceptible than the rest of the tract, for bronchitis, pulmonary congestion and hæmorrhages, coughing and pain in the thorax are induced by quantities that cause little or no irritation of the mouth and nose. Lehmann found that one volume of chlorine or bromine vapor in one million parts of air causes some irritation, but no serious results, but that ten volumes in the same amount of air inhaled for some time, cause hæmorrhage and inflammation of the lungs, severe bronchitis and other similar effects. After fatal poisoning from the inhalation of bromine, he observed marked irritation of the gastric mucous membrane, while this symptom was absent after chlorine. Another point in which bromine differs from chlorine is in its powerful action on the hair, which is rendered soft and gelatinous, and eventually removed entirely by exposure for some time to the vapor.

These symptoms of chlorine and bromine poisoning are caused by their local action only; they are changed to hydrochloric and hydrobromic acids, and these again to chlorides and bromides in the course of absorption. Attention has been drawn to a number of cases in which symptoms arose in workmen in chemical factories where chlorine is liberated by electrolysis, or more rarely in others where hydrochloric acid is formed in large quantities. The most marked symptom is an affection of the sebaceous glands, from which the condition receives its name of chlorine acne, but this often induces headache, sleeplessness, loss of appetite and anæmia. No satisfactory explanation of the symptoms has been given, nor is it known whether the chlorine or some unknown body is the cause (Lehmann, Jacquet).

PREPARATIONS.

Liquor Chlori Compositus (U. S. P.), chlorine water, contains at least 4 parts of the gas in 1,000 parts of water. It is a clear, greenish liquid with the suffocating odor of chlorine and is liable to form hydrochloric acid, especially when exposed to the air and sunlight. It ought therefore to be freshly prepared when the full strength is required.

Calx Chlorinata (U. S. P., B. P.), chlorinated lime, bleaching powder, sometimes erroneously called chloride of lime, is a compound formed by the action of chlorine on lime. It consists of a mixture of calcium hypochlorite ($Ca(ClO)_2$), calcium chloride ($CaCl_2$), lime and water. The hypochlorite is very unstable and gives off chlorine in air, and especially in the presence of an acid. Strong acids also free the hydrochloric acid of the chloride, and this is decomposed by the hypochlorite into chlorine and water. Chlorinated lime forms a white or grayish-white powder, with the odor of chlorine. It is only partially soluble in water and must contain not less than 30 per cent. of available chlorine, U. S. P.; 33 per cent. B. P.

Liquor Calcis Chlorinatæ (B. P.).—The solution should yield about 3 per cent. of chlorine.

Liquor Sodæ Chlorinatæ (U. S. P., B. P.), solution of chlorinated soda, Labarraque's solution or Javelle's solution, is formed from chlorinated lime and contains hypochlorite of soda ($NaClO$) and chloride of soda. Like the corresponding lime salts, it has the odor of chlorine and bleaches vegetable colors. It must contain at least 2.4 per cent. by weight of available chlorine.

Chlorine was formerly used internally in infectious disease, but this has been entirely abandoned, since it has been recognized that it is much more poisonous to the higher animals than to the microorganisms. The inhalation of chlorine in phthisis has also fallen into disuse for the same reason. Chlorine water and the solution of chlorinated soda are still occasionally used as antiseptic, deodorant solutions in the treatment of foul sores, and, more rarely, to disinfect the hands before operation; both preparations are very irritant, however. Chlorine water much diluted has been used as a gargle, as a vaginal injection and for other similar purposes.

The chlorine preparations are chiefly used to disinfect fæces, urinals and to a less extent rooms and houses; for this purpose chlorinated lime is the most suitable, especially when acid is added to it in excess. The room ought to be hermetically sealed, and the fumes are of no value as disinfectants unless they are present in such quantity as to render the air quite irrespirable. They have the disadvantage that they bleach most of the colors used in dyeing, and fail to penetrate in sufficient quantity into the clothing, which they also corrode to some extent. Chlorinated lime exposed in the sick-room merely serves as a deodorant, and has no disinfectant value, but has the disadvantage of giving a false feeling of security like other similar measures. Chlorine seems inferior to sulphurous acid anhydride, and still more so to formalin as a disinfectant, not from its being weaker in action, but because it is more difficult to apply in sufficient quantity. Chlorinated lime can, however, be applied in urinals and closets, where both these disinfectants are unavailable. Here it acts again as a deodorant, while its disinfectant value is smaller.

In **Poisoning** with chlorine taken by the mouth, alkalies are advised with the view of neutralizing the acid formed, and narcotics may be necessary for the pain. In cases of poisoning by inhalation, steam may be inhaled to lessen the irritation, and ammonia has been advised, but is itself irritant. In corrosion of the skin with bromine, one half per cent. carbolic acid has been applied with success, it is said, the bromine being precipitated as bromphenol. Vapor of carbolic acid has also been inhaled in bromine irritation of the nose and throat.

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XXVII. OXYGEN.

Ever since the discovery of the relation of oxygen to the respiration, attempts have been made to use it in therapeutics, by inhaling the gas pure or mixed with air, or by spending a certain time each day in chambers of compressed air. It was expected that by these means a larger amount of oxygen would be absorbed, and a more active combustion in the tissues would be induced. The absorption of oxygen by the lungs does not depend on the partial pressure of the oxygen, however, but on its affinity for the reduced hæmoglobin of the corpuscles. It is true that the oxygen dissolved in the plasma is increased by a great rise in the barometric pressure, or by inhaling pure oxygen, but this dissolved oxygen is trifling in amount compared with that in combination with the hæmoglobin. Under ordinary conditions, then, the air is sufficient to oxidize almost all the reduced hæmoglobin passing through the lungs, and oxygen lessens but slightly the small proportion that escapes by the pulmonary veins unoxidized. As far as the tissues are concerned, the oxidation is of course the same whether the oxyhæmoglobin carried to them by the blood was formed in a pure atmosphere of oxygen or in air, of which it comprises only about 20 per cent. The slight increase in the oxyhæmoglobin of the blood has no appreciable effect, as more oxygen is offered to the tissues normally than they can assimilate. It is therefore inconceivable that the very slight increase in the quantity of oxygen in the blood can have any effect on the oxidation in the tissues under ordinary conditions. But if the gas be inhaled under high pressure the augmented tension in the blood may induce some symptoms, and this is, according to Smith, the explanation of a tendency to tetanic convulsions which he found developed in animals under these circumstances; hilarity and some other nervous effects are said to have been induced in man in some instances, and these may also be interpreted as the results of the high oxygen tension in the blood, if they were not the products of fancy and suggestion. Oxygen inhalation is therefore incapable of increasing the oxidation in the tissues, or in fact of modifying in any way the metabolism, and experience has shown it to be valueless in such constitutional diseases as diabetes and gout, in which, moreover, it has been demonstrated that there is no deficiency in the oxygen of the blood.

The further question arises whether oxygen inhalation is likely to be of benefit in the cyanosis due to severe cardiac or pulmonary disease. Improvement is sometimes observed clinically, the skin losing its dark color, and the respiration and heart becoming less rapid and labored as soon as the inhalation is commenced, and alarming symptoms returning when it is stopped. This may be explained by the larger amount of oxygen dissolved in the plasma; when air is breathed, the plasma contains only about 0.6 per cent. of oxygen in simple solution, but when oxygen is inhaled the percentage may rise to 3 per cent. and this may reinforce the oxygen carried by the hæmoglobin. In cases in which only a small quantity of blood is passed through the lungs owing to circulatory disorder or where the aërating surface of the lungs is diminished by exudation, this small supplementary supply of oxygen may be of importance. Again the air actually inspired does not pass directly into the alveoli, but diffuses from the wider air passages into the narrower ones and then reaches the absorbent surfaces. Pure oxygen diffuses more rapidly and in larger quantity into the alveoli than when it is mixed with nitrogen, and it is therefore conceivable that when the movement of the air in the air passages is insufficient, oxygen may give relief by diffusing in larger quantity into the alveoli. Insufficient movement of the air currents may be due to obstruction of the respiratory tract, as in asthma or severe bronchitis, or to slow and shallow breathing from depression of the centre. Accordingly, the inhalation of oxygen is said to be followed by relief in some cases of asthma and bronchitis, and it has been recommended in narcotic poisoning.

When the hæmoglobin of the blood is so altered as to be incapable of transporting oxygen to the tissues, as in cases of poisoning with carbon monoxide, nitrites, chlorates, nitrobenzol, etc., oxygen inhalation is indicated, for it has been shown by Haldane and others that the plasma dissolves enough oxygen to maintain life when that supplied by the blood corpuscles is insufficient. The inhalation has to be continued until the symptoms of deficient aëration have disappeared.

Many microbes are killed or at any rate much retarded in their growth when freely exposed to the air, and attempts have been made to treat pulmonary phthisis by oxygen inhalation. The results have been less disastrous than those of some of the other treatments by inhalation, but no distinct benefit has accrued, and in some cases hæmoptysis has been induced by it from some unexplained cause. Smith has recently found that the inhalation of oxygen under some pressure causes irritation, congestion and consolidation of the lungs in mice and birds.

Oxygen is inhaled through a mask connected with a large container which is filled from a tank of the compressed gas. Very often the oxygen may be diluted with air and for this purpose a small opening may be made in the mask.

Ozone, or active oxygen (O_3), is a much more powerful oxidizing body than ordinary oxygen, but is more easily reduced than peroxide of hydrogen. It has a curious phosphorous odor and is somewhat irritant to the respiratory membranes, but it is almost always accompanied by nitrogen oxides, and some of the properties which have been ascribed to ozone may be due to these impurities. It is rapidly decomposed by living matter, and it seems very improbable that it can be absorbed into the blood; yet Binz and Schulz believe that ozone induces narcosis in dogs, rabbits and kittens; it does not seem dangerous to inhale it in dilution. Ozone injures most enzymes and the fermentation of yeast is hindered, but the lactic fermentation does not seem to be affected and some others are merely delayed. Ozone applied to the seeds or leaves of the higher plants also delays their development and injures them.

Ozone has undoubtedly disinfectant properties, but these are only apparent when air contains 13.5 mg. or more per litre. Even this disinfects only the air itself and the surfaces of objects, as the ozone loses its oxidizing properties whenever it comes in contact with organic matter and therefore fails to penetrate. It has recently been advocated to disinfect drinking water, but is efficient only in fairly pure waters, as any organic matter is oxidized and thus absorbs the ozone and the microbes escape. For this reason it cannot be used to sterilize milk or food.

Ozone inhalation has been recommended in the hope of increasing the oxidation of the tissues, and as an antiseptic in pulmonary phthisis, but its irritant properties preclude its use here, and it has been generally discarded. It was supposed to be formed in turpentine oil on standing, and old turpentine oil was therefore recommended in cases of phosphorus poisoning, with the hope that it would tend to oxidize the phosphorus and render it harmless. Recent investigations show, however, that no ozone is formed in turpentine oil, and there is no reason to suppose that the treatment is of benefit.

Many so-called solutions of ozone contain only small percentages of hydrogen peroxide and no ozone proper, as, though the latter is soluble in water, it decomposes very rapidly, only traces of it being found in the solution after 10–15 days. It breaks up into oxygen, and does not form hydrogen peroxide.

The ozone of the air has been appealed to, in order to explain and advertise the benefits induced by many watering places and forest resorts, but it has never been satisfactorily proved that the air in these localities contains more ozone than in other less favored places. The curative agency is generally the change of scene and interests and the dietary.

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XXVIII. PEROXIDE OF HYDROGEN.

Hydrogen peroxide or dioxide (H_2O_2) tends to break down into water and oxygen very rapidly in the presence of many substances, which in themselves may be either oxidizing or reducing. Among the bodies which induce this decomposition are the peroxidase ferments, which are found in all forms of living matter, and the peroxide of hydrogen is therefore decomposed when brought in contact with the tissues; the oxygen thus liberated tends to oxidize its surroundings and its chief effects are therefore due to its oxidizing properties. It is generally met with in dilute solution in water, and in this form alone is used in medicine. Brought in contact with the skin, peroxide of hydrogen solution is decomposed, and numerous bubbles of oxygen are formed,[1] but this decomposition proceeds much more rapidly when it is applied to denuded surfaces or to mucous membranes. The oxygen is formed in such quantity that some irritation may follow, and thus dogs often vomit when it is administered in quantity by the mouth. When it is injected subcutaneously, a large amount of oxygen is formed in the subcutaneous tissues, but some of the peroxide escapes decomposition and is absorbed into the blood. Here the decomposition proceeds more violently, the red blood cells having a strong catalytic action, and the oxygen set free may cause emboli and lead to sudden death. The formation of emboli is seen most frequently in the rabbit, but was in all probability the cause of death in one case of fatal poisoning in man, in which a solution of hydrogen peroxide had been used to wash out the pleural cavity.[2] Emboli are not formed in the dog on hypodermic injection, nor in either dogs or rabbits poisoned by the stomach—in the latter case probably because the liquid is more slowly absorbed and is almost entirely decomposed in the mucous membrane. Even in the blood and tissues the whole of the peroxide is not decomposed, for several observers have found traces of it excreted in the urine.

Injected intravenously in either dogs or rabbits the peroxide is rapidly decomposed in the blood, and forms emboli which prove immediately fatal by stopping the circulation through the lungs, heart and brain.

The catalytic decomposition of the peroxide occurs also in excised organs and in drawn blood as long as the ferment is not destroyed. The different organs vary considerably in their catalytic power, the red blood cells and the liver cells being the most active.

The catalysis of hydrogen peroxide occurs in the lower forms of life as well as in the higher. Thus germinating seeds, yeasts, infusoria and the microbes all free oxygen from the solution, and in fact, a rough estimate of the number of microbes in water may be formed from the amount of oxygen given off by it on the addition of the peroxide (Gottstein). This decomposition is fatal to most of these lower forms, presumably from the nascent oxygen, and peroxide of hydrogen is therefore a powerful disinfectant, a three per cent. solution proving as strongly bactericidal as a one per mille solution of corrosive sublimate; but when the microbes are contained in a medium with much organic substance, as in wounds, the bactericidal action is very much reduced. This appears to be due to the too rapid decomposition of the peroxide, which escapes as bubbles of oxygen, comparatively little oxidation taking place. This may be exemplified by its action on the blood; when normal blood in a test-tube is treated with peroxide, it froths up and the oxygen escapes, leaving the blood unaltered. If, however, some hydrocyanic acid has been added to the blood sometime previously so as to weaken the ferment, there is little or no effervescence and the hæmoglobin is changed to methæmoglobin by the peroxide remaining and freeing its oxygen more slowly.

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[1] A concentrated solution is said to corrode the skin, leaving a white eschar.

[2] In several other instances hemiplegia has been observed, apparently from embolism of the cerebral arteries.

In recent years, attention has been drawn to other bodies analogous to hydrogen peroxide, some of which possess powerful microbicidal properties. The peroxide is represented by the structural formula H—O—O—H and one of the hydrogens may be replaced by benzoyl or acetyl, forming $C_6H_5CO—O—OH$ (benzo-peracid) or $CH_3CO—OOH$ (aceto-peracid). These have been shown to be much more powerful germicides than hydrogen peroxide, while they give off oxygen less readily; in fact they are comparable only to corrosive sublimate in their destructive effect on microörganisms and even surpass it in favorable conditions. The slow evolution of oxygen by these bodies explains their action being more powerful than that of hydrogen peroxide. The peracids are prepared with difficulty and are very unstable bodies, so that it is unlikely that they will prove of value in practical medicine. But they are formed when the aqueous solutions of some more readily available substances are allowed to stand for some time. In these, both the hydrogen atoms of hydrogen peroxide are replaced by organic radicles, forming organic peroxides such as diacetyl peroxide ($CH_3CO—O—O—COCH_3$) and benzoyl-acetyl-peroxide ($C_6H_5CO—O—O—COCH_3$). On dissolving these in water, the peracids are formed and the solutions are very powerful disinfectants, which have been suggested for surgical use and also as intestinal disinfectants; practical clinical experience alone can decide whether they possess that value which the results in the laboratory seem to indicate.

PREPARATIONS.

Aqua Hydrogenii Dioxidi (U. S. P.), *Liquor Hydrogenii Peroxidi* (B. P.), solution of hydrogen dioxide or peroxide, contains about 3 per cent. by weight of the pure dioxide. Each volume of this solution is capable of setting free 9–11 volumes of oxygen when completely decomposed. Some acid is added to the peroxide solution in order to retard its decomposition, but it gradually changes when kept, so that only freshly prepared solutions are of full strength. The solution is colorless and odorless, but has an acid taste from the added acid, and the oxygen freed in the mouth gives a curious sensation and forms a froth.

Therapeutic Uses.—Hydrogen dioxide is used locally as a disinfectant solution in suppuration, diphtheria and urethral infection. In pus cavities the oxygen is freed with great rapidity, and the pus-corpuscles are said to be disintegrated. The catalysis is due in part to these corpuscles, in part to the microbes, and the extent of the suppuration may be estimated from the amount of effervescence. Peroxide solutions differ from most other disinfectants in the short duration of the action, which passes off as soon as all the oxygen is liberated. In addition to its microbicidal action proper, this agent loosens and destroys masses of infected material by the mechanical effect of the liberation of the gas, and the wound or cavity is thus cleaned by it more perfectly than by washing with ordinary antiseptic solutions. The solution has been recommended for use in ophthalmic practice, and for this purpose may be diluted one half.

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Other Oxidizing Disinfectants.

Other oxidizing bodies have been used as antiseptics and disinfectants. Thus *Calcium Peroxide* or *Gorit* has been recommended as a gastric and intestinal disinfectant for children in doses of 0.2–0.6 G. in milk. Zinc peroxide and magnesium peroxide have also been suggested, the former for external, the latter for internal use.

Similarly the *Persulphates* of potassium and sodium ($Na_2S_2O_8$), *persodine*, possess strong oxidizing properties from their liberating oxygen in contact with organic matter. They are only feebly poisonous but have not been extensively used as yet.

Some older and better known disinfectants also owe their powers to liberated oxygen, and among these that most largely employed is the *Permanganate of Potassium.*

When a solution of this salt comes in contact with organic matter, such as albumin, the permanganate at once parts with some of its oxygen, which attaches itself to the albumin. Permanganate is thus poisonous to protoplasm, not through the presence of the whole molecule, but in consequence of the oxidation of the proteids. As soon as the permanganate is reduced, it of course loses this action, so that the oxidizing effect is limited to the skin and the surface of the mucous membranes. Concentrated solutions irritate, and even corrode the skin, and induce gastro-enteritis when swallowed. Permanganate solutions are disinfectants of considerable power, owing to their oxidizing and thus destroying bacteria. They fail to penetrate deeply in an active form, and this renders them of less value than many other disinfectants, except in very superficial infection.

PREPARATIONS.

Potassii Permanganas (U. S. P., B. P.) ($KMnO_4$) forms slender crystals of a dark purple color and a sweetish, afterwards disagreeable and astringent

acts on certain phases of metabolism; not local or spec. organ actio
Very insol. - so passes thru tract, unless given in finely
divided state or in sol. in oil - then fatal in very small doses (.05 - .1

taste, soluble in sixteen parts of water, reduced by alcohol and other organic bodies. 0.05–0.2 G. (1–3 grs.), in pills made up with kaolin.

Therapeutic Uses.—The permanganate has been used internally in amenorrhœa and chlorosis.

Externally it is used for its disinfectant and deodorant action, as an application to gangrenous ulcers, cancerous sores, diphtheria, and gonorrhœa. In dilute solution it may be used as a gargle and mouth wash (1 per cent.), to disinfect the hands (1–3 per cent.), which it stains brown, and for other similar purposes.

It has recently been recommended in poisoning with phosphorus, prussic acid, morphine and other alkaloids, on the theory that these poisons are oxidized by it in the stomach, and thus rendered harmless. For this purpose it is given in one-third per cent. solution. It may be questioned whether much permanganate reaches the stomach unreduced, and the method is certainly less reliable than the stomach tube. Only the poison actually in the stomach is destroyed, permanganate having, of course, no effect upon that absorbed into the blood. In snakebite, permanganate has been advised, and it undoubtedly has some action on the poison when it comes in contact with it, and may therefore be used to wash the wound and also to inject around it; it has no effect upon the poison already absorbed.

Condy's Fluid is a strong solution of impure permanganate, which is of use to disinfect and deodorize urinals and fæces, but must be poured on them, and cannot be employed to disinfect rooms.

Some of the caustics owe part of their action to the oxygen liberated when they come in contact with organic matter. Thus *Chromic Acid* destroys tissue in part through its acidity but this is reinforced by its oxidizing powers.

XXIX. PHOSPHORUS.

In the early part of last century phosphorus played a very important rôle in therapeutics, and, in fact, was regarded almost as a panacea, but at present its use is much more restricted, and some doubt is entertained as to its possessing any therapeutic value whatever. At the same time, it has been the subject of much and laborious investigation, partly because it has frequently given rise to poisoning, and partly because the study of its effects has thrown much light on some physiological and pathological processes. It differs from most poisons in acting for the most part on certain phases of the animal metabolism, and in having comparatively little direct action at the point of application, or, indeed, upon any single organ.

Phosphorus is absorbed with difficulty, because it is very insoluble in water and the body fluids and is only slowly volatilized at ordinary body temperature. Large masses of phosphorus may thus pass through the alimentary canal without serious effects, because they fail to be dissolved and absorbed. But when it is taken in a finely divided condition or in solution in oil, it gives rise to symptoms in very small

In suicide – rat poison or 20 match heads. Absorbed by lungs as vapor. Not absorbed from skin (burns etc) yel more poisonous than red, as more volatile + soluble. P in blood as such. No action when oxidized (acids etc). Swallow – in 2 hrs, stomach pain, garlic odor, vomit diarrhoea. Vomit for 2 days then abd pain jaundice weakness, haemorrhages, coma. Prognosis [illegible] fatal

quantity, and has been found to induce fatal poisoning in man in doses of 0.05–0.1 G. (1–2 grs.).[1] In these conditions it is absorbed partly as vapor, partly in solution in water, which dissolves only traces, however, and probably chiefly in solution in the fats and oils, in which it is much more soluble. Phosphorus vapor is also absorbed by the lungs, and the symptoms of chronic poisoning in match factories are believed to arise in this way. It does not seem to be taken up from the skin, and has in fact little effect unless when rubbed on it, when it ignites and gives rise to severe burns; phosphorus burns do not cause phosphorus poisoning, however, as is sometimes stated. The red amorphous phosphorus is much less poisonous than the ordinary yellow form, because it is less soluble and also less volatile, and consequently fails to be absorbed.

Phosphorus exists in the blood as such, and the effects on the tissues are unquestionably due to the element itself, and not to the oxygen or hydrogen compounds, as has been supposed. Some phosphuretted hydrogen (PH_3) may be formed in the bowel, but is comparatively unimportant, the great mass of the phosphorus being absorbed unchanged. As soon as it is oxidized, phosphorus loses its specific action, all of the acids being comparatively harmless. Phosphorus has been detected in the blood, and, it is said, in some of the excretions.

It is devoid of action on albumins in solution and has no immediate irritant effects, such as are seen in poisoning with the heavy metals.

Symptoms.—When a poisonous dose of phosphorus is swallowed, no effects are elicited as a general rule for several hours. The first symptoms are pain and discomfort in the region of the stomach, nausea and eructation of the vapor with its characteristic garlic odor, and then vomiting, the contents of the stomach having the same odor, and being phosphorescent in the dark. Later, bile may be vomited, and some diarrhœa may set in, although this is not a common symptom. The nausea and vomiting often continue without further symptoms for several days, but frequently disappear, and the patient apparently recovers, particularly if the dose has been small, or if most of it has been removed by vomiting or by washing out the stomach. In the course of a few days, however, the symptoms recur, and are generally accompanied by some jaundice; the pain extends from the stomach to the liver, and soon to the whole of the abdomen. The vomited matter no longer contains phosphorus, but may be bloody. The patient complains of general weakness and faintness; the pulse is weak, the liver extends far below the ribs, and the urine shows characteristic changes (see page 604); hæmorrhages occur from the nose, bowel, uterus and under the skin, and eventually a condition of collapse and fatal coma follows. Convulsions and delirium have been observed in a considerable proportion of cases towards the termination of the intoxication. Death may occur, however, in the first stage or

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[1] Phosphorus is often used in suicide, generally in the form of rat poison or of match heads. Each phosphorus match is estimated to carry 3–5 mg. of phosphorus, so that 15–20 match heads are sufficient to induce fatal poisoning.

P fumes = periostitis + mandible necrosis carious tooth or gum le
Pus + sequestrum. Fatty degeneration. liver kid. all muscle. Is unusual deposition of normal preformed fat

early in the second, before complete exhaustion is reached, and in these cases would seem to be best explained by the direct action of the poison on the heart. If only a small quantity be swallowed, or if active therapeutic measures be taken early, the patient may recover without any secondary symptoms, and even when these have followed the prognosis is not hopeless, for the symptoms slowly disappear in a certain proportion of cases.

Exposure to the fumes of phosphorus has long been known to give rise to periostitis and necrosis of the lower jaw. The disease begins from a carious tooth or from some lesion of the gum, and may involve most of the jaw, which becomes swollen and painful and eventually evacuates large quantities of pus with pieces of dead bone. This necrosis was formerly frequent in match factories, but has become rarer since amorphous phosphorus has been substituted for the yellow form,[1] and since greater attention has been paid to the ventilation of the factories and to the condition of the teeth of the employees. Magitot has recently advanced the opinion that exposure to phosphorus fumes gives rise to a mild chronic form of poisoning, quite aside from the necrosis, which is comparatively rare. The symptoms are cachexia, slight jaundice, anæmia and abuminuria, and in more advanced cases chronic enteritis and diarrhœa, bronchitis and a curious fragility of the bones.

Action: Fatty Degeneration.—A very striking feature in phosphorus poisoning, and one that was early recognized in its history, is the appearance of numerous fat globules in the cells of many organs, notably in those of the liver, kidney, gastric and intestinal glands, and in the muscle fibres of the heart, stomach, intestine, smaller arteries and often of the skeletal muscles. This fat was formerly believed to be formed by the degeneration of the proteins of the cells in which it is found, but it appears that it is really ordinary fat transported from the positions which it normally occupies and deposited in the cells of the liver, heart and other organs. Pflüger has shown that the total fat of the body is not increased by phosphorus, and Rosenberg found that when an animal has been fed on foreign fats (*e. g.*, a dog upon mutton suet) and is then poisoned with phosphorus, the fat found in the liver cells is that characteristic of the food and not that of the poisoned animal as might be expected if it were derived from the proteins. Further, Leathes has shown that the fat found in the liver in phosphorus poisoning possesses the characteristics of fat ordinarily found in the subcutaneous deposits and not that of the fat of organs, so that there is every reason to regard it as normal preformed fat deposited in unusual position, rather than as a new product of the intoxication. The fatty infiltration sets in only after some time, and, in fact, accompanies the secondary symptoms for the most part, although the cells of the stomach and upper part of the intestine suffer sooner, and the first. Cloudy swelling then granules → fatty degen → detritus; Chronic poisoning – proliferation of interstitial ct. of stomach, liver & kid cirrhosis with dropsy. anaemia, cachexia. dose $\frac{1}{10}$–$\frac{1}{5}$ mg = stim to osteoblasts of long bones see ✓

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[1] The phosphorus sesquisulphide (P_4S_3), recently introduced in match factories, seems to be even safer than red phosphorus, for though minute quantities of the element are released from it in the tissues, these are too small to induce any symptoms.

beginning of this process is probably the cause of the early vomiting. The process commences in cloudy swelling of the cells, followed by the appearance of granules, which soon develop into fat globules. Eventually the degenerated cells break up into detritus.

Another feature in phosphorus poisoning, which is, however, better seen after repeated small doses than after a single large one, is the **Proliferation of the Interstitial Connective Tissue** of the stomach, liver and kidney, which finally induces typical cirrhosis of these organs. It was formerly supposed that this indicated a specific irritant action of the phosphorus vapor on the connective tissue, but many pathologists now regard this proliferation as a secondary result of the necrosis of the parenchyma cells. In animals poisoned by the prolonged administration of small quantities of phosphorus, the ordinary effects of hepatic and renal cirrhosis have been induced, such as dropsy, anæmia and cachexia.

Besides the cells which have undergone fatty degeneration, the liver often contains numerous microscopic areas of necrotic tissue and in other parts actively dividing parenchymatous cells, and these appear to replace those which have succumbed to the poison, when recovery follows.

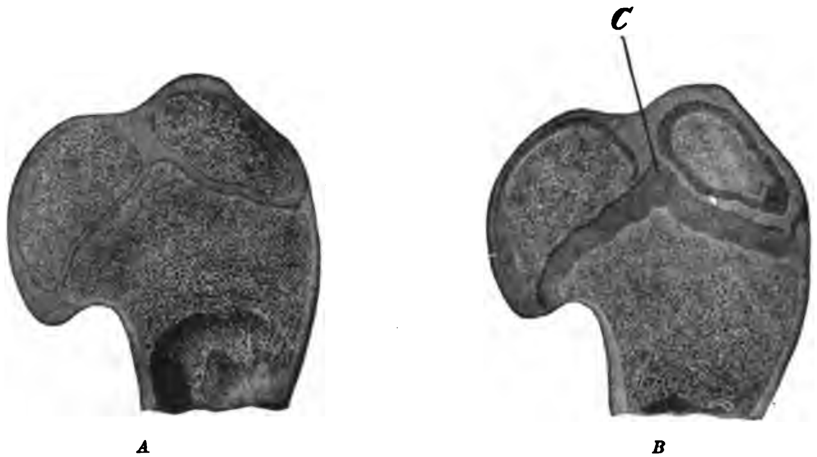
When very minute quantities of phosphorus are administered to animals, no poisoning results, but according to Wegner, a specific action on the **Bones** is induced, especially in young animals, in which the bones are still growing. Thus, in young rabbits, quantities of $\frac{1}{10}$–$\frac{1}{5}$ mg. given for several weeks are found to be followed by characteristic changes in the growth of the long bones, apparently induced by the phosphorus acting as an irritant or stimulant to the bone-forming cells (osteoblasts). ✓ Wherever cancellous bone is being formed from cartilage, phosphorus is stated by Wegner to cause the deposit of a layer which resembles the dense bone of the shaft in the normal animal in general appearance and also histologically. This layer of dense bone at the growing point is at first the only change induced, but if the treatment lasts longer the soft cancellous bone which was deposited before the phosphorus treatment began is gradually absorbed. The medullary cavity of the bone is thus enlarged, and may, in fact, extend into the epiphyses, which in the normal bone are filled with cancellous tissue, but which now form part of the much lengthened cavity. Eventually the whole of the cancellous bone may be absorbed and a similar process of absorption begins in the bone formed at first under phosphorus, while the dense deposit is pushed further into the remaining cartilage. The development of bone from cartilage is not the only process affected, however, for Wegner states that in the bone deposited from the periosteum a somewhat similar change is induced, as is shown by its becoming denser and by the Haversian canals being much contracted in size. In full-grown animals the changes in the bone are much less distinct, but the lamellæ of the spongy tissue are said to be thickened by phosphorus treatment, and in the fowl Wegner states that the medullary cavity may be completely obliterated by the

Small doses — much hard bone. Large doses — much eating of bone.

deposition of hard bone. Wegner supposes that this effect on bone is due to a specific action on the bone-forming cells, analogous to that which he observed in the connective tissue of the liver. As has been mentioned already, however, the cirrhosis of the liver in chronic phosphorus poisoning is believed by many not to be due to primary irritation of the interstitial tissue, but to be secondary to the destruction of the parenchymatous cells, so that this analogy is rendered doubtful.

Wegner found further that when the calcium salts were withdrawn from the food of animals treated with phosphorus, the exaggerated activity of the bone-forming cells continued, but no lime was deposited, so that the bone presented the appearance of rickets. The same result has, however, been obtained by other investigators by the withdrawal of calcium without phosphorus. Kassowitz took up the investigation some twelve years later, and observed the layer of white dense bone described by Wegner at the edge of the ossifying cartilage, but regards it not as the result of excessive activity of the osteoblasts, but as due to a slower absorption of the calcified cartilage from a less rapid extension of the blood vessels than is normal. With large doses he produced appearances closely resembling those of rickets. Several other investigators have observed changes in the bones after phosphorus, so that there is good reason to believe that it possesses some specific action on them, bones although some writers failed to obtain definite results and of those who observed a modification in the growth no two agree in the description of the changes or in their interpretation. This specific action on the bone-forming tissues and particularly on the periosteum may explain the necrosis of the jaw in match factories. The view of the latest investigators is that microbial infection is necessary to permit of the changes observed clinically, but that phosphorus

FIG. 61.



Section of the head of the femur in calf. *A*, normal; *B*, after treatment with minute doses of phosphorus; *C*, the cap of dense bone at the growing point. (After WEGNER.)

lowers bone's resistance + tract infection easier - the immediate death
acts directly on heart. If patient lasts by degeneration of heart. fatty deg.
art. walls — haemorrhages (also fibrinogen destroyed by liver + intest)

induces some change in the bones which predisposes them to infection by the tubercle bacillus and other organisms which induce necrosis. The occurrence of necrosis of the jaw is in fact a strong argument for the correctness of the view that a specific action on bone exists, for under no other poison, even when much more irritant vapor is inhaled, does a similar process occur in man. And a further argument for this specific action is the fragility of the bones which occurs in a considerable percentage of workers in match factories. Here the phosphorus is carried to the bones (femur, tibia, radius, etc.) in the blood and there is no possibility of its reaching them directly as in the case of the jaw. It seems probable therefore that in phosphorus necrosis of the jaw the bone is changed by the phosphorus absorbed and carried to it by the blood and that this change predisposes to infection through a diseased tooth or sinus. The exact nature of this action on bone and its relation to rickets and to osteomalacia must, however, be left for further research to determine.

Phosphorus weakens and slows the **Heart** when it is applied to it directly in the frog, or by intravenous injection in mammals. In many cases of acute poisoning in man, however, the heart does not seem to be seriously affected until very late, and this is particularly the case when comparatively small quantities have been absorbed. In those cases in which large amounts are swallowed in solution or in fine division, and in which death occurs before any secondary symptoms have been developed, the fatal issue is generally ascribed to the cardiac action. This direct action on the heart must be distinguished from the fatty degeneration of the cardiac muscle, which is seen in the later stages of poisoning, for no degeneration of the heart, and, in fact, no pathological changes whatever, may be found in those rapidly fatal cases. Phosphorus acts on the heart muscle directly, and does not seem to affect the regulating nerves in any way.

The **Blood** is but little changed outside the body by phosphorus, for though Araki states that the hæmoglobin parts with oxygen more slowly than usual, the difference is trifling. In many cases of fatal poisoning the blood is found not to clot so readily as usual, and sometimes to remain fluid for forty-eight hours or more. According to Corin and Ansiaux and Jacoby this occurs only in cases in which the patients live for several days, and is not a direct effect of the poison, but is due to the changes in the intestine and liver, which lessen or entirely destroy the fibrinogen. Jacoby states that the blood not only fails to clot but is capable of redissolving fibrin and attributes this to the presence of the autolytic ferment of the liver.

The absence of clotting in the blood may be a factor in the hæmorrhages which are met with among the symptoms of the second stage, but the immediate cause of these is the fatty degeneration of the muscular coat of the smaller arteries throughout the body. These changes in the blood vessels may perhaps explain the œdema of the retina, which is seen in animals poisoned with phosphorus, though these have also been attributed to some change in the blood. Occa-

Reds increased. white decreased. atrophy of marrow, fibrosis. Nerv. syst unaffected. Coma from disordered metabolism. Gi epith degen = pain vomit & diarrhoea. Fat inf. of liver = jaundice

sionally gangrene of the extremities has been observed in phosphorus poisoning, probably owing to the changes in the vessel walls.

Small doses of phosphorus generally increase the number of the red-blood cells in man, and even in poisoning a sudden or gradual increase in these may occur, along with a diminution of the leucocytes. The hæmoglobin is not correspondingly augmented, however. In the lower animals the effect on the blood cells varies a great deal; in the dog an unusual number of red-blood cells appears to be destroyed; in the rabbit no distinct alteration in the number of the red cells but some leucocytosis has been observed, while in fowls an increase in the leucocytes accompanies a marked destruction of the red cells; in the frog the number of red cells is not reduced.

The **Bone-marrow** in chronic poisoning is at first hyperæmic, the fat cells are atrophied and the leucoblasts are greatly increased; later a gelatinous degeneration sets in with a decrease in the number of the marrow-cells and a corresponding increase in the connective tissue.

The peripheral **Nerves** and **Muscles** do not seem to be affected in phosphorus poisoning, except in so far as the latter undergo fatty degeneration. An excised muscle lives almost as long in salt solution containing phosphorus as in the unpoisoned solution.

The **Central Nervous System** is also little changed by phosphorus. The coma and convulsions which appear before death may be due rather to the disordered metabolism than to any direct influence, as is shown by the fact that consciousness is preserved throughout the first stage, and as a general rule until late in the second.

The fatty degeneration of the epithelial cells of the **Stomach and Intestine** explains the abdominal pain, the vomiting and the occasional diarrhœa seen among the secondary symptoms. The earlier phases of this action may be the cause of the vomiting and nausea of the first stage. This degeneration occurs also when phosphorus is injected hypodermically, and is therefore of the same nature as that in the other organs. The cells of the stomach first attacked are those of the glands, and the condition has been termed gastradenitis.

The fatty changes in the **Liver** cause a considerable increase in the area of hepatic dulness, and at the same time induce some pain and tenderness over the organ.

In the earlier phases the secretion of ~~bile pigment is increased,~~ denoting an unwonted activity of the liver, but later as the cells become infiltrated with fat, they press on the bile capillaries and occlude them so that the bile is absorbed into the blood vessels and gives rise to jaundice. The secretion at this stage is clouded, viscous and not deeply pigmented, and appears to be derived mainly from the mucus cells of the smaller bile ducts and not from the liver cells proper. During recovery the cells lessen in size and cease to press on the ducts, and the bile loses its turbidity and viscosity, and is very dark in color, because the pigment which was deposited in the tissues during the second stage is reabsorbed and excreted; the jaundice color of course disappears from the skin as the bile pigment is reabsorbed.

Bile pigment increased. Metabolic liver changes. Proteins ⇒ amino acids marked; these combine with NH_3. Polyuria then anuria.

The bile salts are very much reduced in phosphorus poisoning. The jaundice may also be accounted for in part by the destruction of the red cells of the blood and consequent increase of pigment formation in the liver. This view is supported by the fact that in the rabbit, in which the red cells are not decomposed by phosphorus, no icterus is observed, while in the dog, in which some of the cells are destroyed, it is very marked. In man, however, there is no evidence that the red cells are diminished in number, yet jaundice is one of the commonest symptoms. The bile very often contains albumin in considerable amount, and in the later stages red blood cells may occur in it.

Other changes have been shown to occur in the liver in phosphorus poisoning; thus the proportion of water is increased while the glycogen and lecithin are reduced. When the distribution of the nitrogen is examined, it is found that a smaller proportion than usual is combined in the form of proteins, while a larger percentage is found in the form of simpler bodies such as ammonia and the amino-acids. The hexon bases are also present in less proportion than normally. When the liver of an unpoisoned animal is kept from putrefaction for some time, the tissue is broken down by the action of an autolytic ferment, and the same constituents are formed in large quantity; the liver in phosphorus poisoning undergoes the same changes when preserved from putrefaction, but the autolysis progresses much more rapidly. Jacoby therefore infers that phosphorus augments the activity of the autolytic ferment of the liver and thus reduces the proteins, glycogen and lecithins, while increasing the simpler amino-acids. The acid formed in this process combines with ammonia. The ferments which decompose the amino-acids do not seem more active in phosphorus poisoning or in autolysis than normally, but only those which decompose the proteins to their simpler bodies. He regards the disappearance of the fibrinogen of the blood as a further effect of this liver autolysis, for he found that the injection of the autolytic ferment into normal animals prevented coagulation.

In the **Kidney**, the fatty degeneration of the epithelium may account for the albuminuria, which is not generally severe, and is not infrequently absent in cases of poisoning. Fatty casts and even globules of fat are often found in the urine in cases which run a chronic course. Blood and hæmoglobin may also appear in it from hæmorrhages into the kidney. The urine itself is often somewhat increased in quantity in the early stages of the intoxication, but afterwards becomes deficient, and towards death complete anuria may be observed. The increased urine is probably due to the increase of the urinary substances in the blood, while the diminution, which may occur early, may be explained by the small quantity of water absorbed from the stomach and intestine; for the same reason the chlorides are much reduced in amount.

The nitrogen of the urine varies considerably in different cases. Very often in the first few days after the ingestion of the poison, it is markedly diminished in amount from the prolonged nausea and vom-

Poison augments N waste. NH_3 increased over urea due to a of excess of lactic (failure to [illegible] ch. beyond) · With icterus, urine dark due to excretion of bile pigment.

iting which prevent the absorption of food; the nitrogenous excretion thus corresponds to that during the first few days of starvation. After this, however, a very considerable increase in the nitrogen is observed, even although the patient continues to fast. In the course of starvation a rise in the nitrogen excretion also occurs after some time, but this is never so great as that seen in phosphorus poisoning, so that the poison evidently augments the waste of the nitrogenous tissues. The excretion of urea does not increase in proportion with the total nitrogen; in fact, less urea is often excreted than in the first days of the intoxication. But the nitrogen excreted in the form of ammonia is much increased in man and the dog, while it is not altered in the rabbit. This excretion of ammonia suggests the formation of excess of acid in the tissues,[1] and as a matter of fact sarcolactic acid is found in very considerable quantity in the urine. The increased ammonia of the urine is therefore to be referred, at any rate in part, to the formation of this acid in the tissues, and if fixed alkalies are administered, the ammonia of the urine falls at once in amount because the alkali neutralizes the sarcolactic acid.

The uric acid excreted is often somewhat increased in amount, but on the whole is little altered by phosphorus in man, which may indicate that the nuclei of the cells are less subject to the action of the poison than the cytoplasm.

Some increase in the other nitrogenous constituents of the urine also occurs in phosphorus poisoning, and a number of amino-acids have been identified in it. The best known of these are tyrosin and leucin crystals, which are not always present in the urine, however, although they have been found in the blood in some quantity. Baumann found an increase in the substances of the aromatic series in the urine. The phosphates of the urine are often very considerably augmented, but not because of the excretion of phosphorus as phosphates, for the quantity absorbed is too small to cause any appreciable change. The increase in the phosphates is rather to be ascribed to an augmented waste of the tissues, and the sulphates are also excreted in larger quantity for the same reason.

When icterus is present, the urine may be dark in color from the bile pigment excreted, and bile acids are also often contained in it.

Metabolism.—The carbonic acid excretion and oxygen absorption by the lungs are generally found to undergo comparatively slight changes in phosphorus poisoning, while all the evidence points to grave derangement in the protein metabolism. Meyer found the alkalinity of the blood reduced through the presence of lactic acid in excess in the tissues, and this has the further effect of increasing the ammonia of the urine; lactic acid is also found in the stomach along with hydrochloric acid. It is believed to arise from the glycogen of the liver, which is much reduced in amount. The great similarity between the results of normal autolysis and of phosphorus poisoning has led to the view that the essential effect of phosphorus is an acceleration of

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[1] See Ammonia, p. 557; Acids, p. 562.

[illegible]
in liver. Incomplete products in excretions. May (cause fatty degeneration. P to phosphoric acid or in organic comb.) fatty deg. of fetus

PH₃ very poisonous.

the autolytic process, and this is supported by the results obtained in experiments in which the autolysis of the normal liver was compared with that of the liver obtained from an animal poisoned with phosphorus.

Autolysis or destructive metabolism occurs in normal living cells, but in phosphorus poisoning it is supposed to proceed more rapidly, and many of its products are not so completely decomposed as normally, so that intermediate products, such as leucin, tyrosin and other amino-acids appear in large quantities in the organs and often in the excretions; lactic acid is similarly a product of autolysis, which fails to be oxidized to carbonic acid as in the normal body. This accelerated autolysis occurs not only in the liver but also in other organs, although in a less marked degree.

It seems probable that the fatty degeneration is a secondary result of the accelerated autolysis; the cells are supposed to absorb fat from the blood more rapidly than normally and to store it in their interior in the form of globules, and as the fat of the blood is thus reduced the normal fat deposits in the body are drawn upon to replace it and this results in the transference of fats from the subcutaneous tissues to such organs as the liver, kidney and heart. But these have lost to a large extent their normal capacity of decomposing fats, which are therefore deposited in the cells in the same forms as occur in the normal adipose tissue.

In view of the curious effect of phosphorus on the tissue change of the vertebrates, its action upon simpler forms possesses some interest. It has been found, however, that yeast, infusoria and bacteria are very little affected by the presence of this poison, and living microbes are found in large numbers on solid pieces of phosphorus. The ferments are also unaffected for the most part, pepsin and pancreatin acting in the presence of phosphorus. The synthesis of hippuric acid in the kidney is lessened if to the blood used to perfuse the organ some phosphorus is added.

The **Temperature** is often low in the later stages of phosphorus poisoning, but slight fever is also observed in some cases.

The **Fate** of phosphorus in the body is still obscure. It is possible that some of it is oxidized to phosphoric acid, and some phosphorus is said to be excreted by the lungs, although the statement that the breath becomes phosphorescent seems to be extremely improbable. It is also excreted in the urine in some organic combinations, of which nothing is known, though they are said to be volatile. In pregnant animals poisoned with phosphorus the fœtus is found to undergo fatty degeneration, so that the poison would seem to pass through the placenta. Phosphorus injected hypodermically acts much more slowly than when swallowed.

Phosphuretted hydrogen (PH_3) induces the same symptoms as phosphorus, when it is given in repeated small quantities. Larger doses are very rapidly fatal and the symptoms differ entirely from those of phosphorus poisoning, consisting of marked dyspnœa, purga-

P — garlic odor — on fire — little sol in H_2O. very in oils ½–1 mg.
Th. Us — in nervous diseases. In rickets, osteomalacia, fractures
In poison: absorbed slowly, so purge, emesis

tion, weakness, tremor, and finally violent convulsions and respiratory failure. The oxygen compounds do not seem to have any such effects, and for the most part are harmless except in very large doses.

PREPARATIONS.

Phosphorus (U. S. P., B. P.), a translucent, nearly colorless solid resembling wax in lustre and consistency. It emits white fumes in the air, which are luminous in the dark and takes fire spontaneously. The fumes have the odor of garlic and in dilute solution phosphorus has a harsh, disagreeable taste. It is very little soluble in water, more so in alcohol, and dissolves to about two per cent. in fats and oils. ½–1 mg. ($\frac{1}{100}$–$\frac{1}{60}$ gr.) (B. P. $\frac{1}{100}$–$\frac{1}{20}$ gr.).

½–1 mg

Oleum Phosphoratum (B. P.) is a one per cent. solution in almond oil and ether (1–5 mins.). Phosphorated oil ought to be freshly prepared and kept in tightly stoppered bottles; solutions of one per cent. tend to lose their strength by evaporation of the phosphorus and by oxidation, when the bottle contains air. It is said to keep better in more dilute solution (one per mille). It is probable that much of the oil dispensed is under one per cent. in strength.

Pilulæ Phosphori (U. S. P.), each pill contains 0.6 mg. of phosphorus ($\frac{1}{100}$ gr.). Dose, 1 pill.

Pilula Phosphori (B. P.), 2 per cent., 1–2 grs.

Therapeutic Uses.—Phosphorus has been recommended in various diseases of the central nervous system and in neuralgia, but it is still questionable whether it is of any real benefit in these. There is more reason to believe in its virtues in bone disease, more especially in rachitis and osteomalacia, for in a number of instances marked improvement has been observed in these diseases under its use. It is generally given in solution in cod-liver oil, and the benefit may be due in part to the menstruum, but not entirely, for Sternberg observed a relapse in a case of osteomalacia when pure cod-liver oil was substituted for the phosphorated oil. In rickets a solution containing 0.01 G. in 100 c.c. of cod-liver oil is recommended; 2–4 teaspoonfuls to be given each day.[1] In osteomalacia a 1 per cent. solution may be prescribed and 1–5 mg. phosphorus taken each day. A number of observers have found that in cases of rickets and osteomalacia more lime was retained under phosphorus treatment than usual, the proportion of the lime of the food which was excreted falling rapidly.

Other bone diseases, such as caries and ununited fractures, have also been treated with phosphorus occasionally, but the results have not been recorded in sufficient numbers to allow of any statement as to the efficacy of the treatment.

Treatment of Phosphorus Poisoning.—Phosphorus is comparatively slowly absorbed from the alimentary canal, so that in the early stages an attempt ought to be made to remove it by emetics or the stomach tube, and by purges. Fats and oils must be avoided, as they tend to dissolve the poison and promote its absorption. Phosphorus has been found in the stools three days after its ingestion, and a sharp purge may therefore be of use up to this time.

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[1] This would be equivalent to ½–2 mg. of phosphorus daily, but as a matter of fact the phosphorated oil from which the prescription is filled contains much less than one per cent., so that the dose actually taken probably seldom amounts to more than one milligram daily.

$CuSO_4$ an emetic + forms insol. [illegible]
$KMnO_4$ to oxidize P. In later stages, alkalis for the lactic.
Surgery for necrosis

Another method of treatment is that aiming at the oxidation of the phosphorus in the stomach, or at the formation of unabsorbable compounds. Turpentine oil was formerly used with the object of oxidizing the phosphorus or of forming some compound with it in the stomach, but this treatment has proved quite valueless (Plavec). Sulphate of copper is recommended in phosphorus poisoning, a large dose being given first as an emetic, and afterwards smaller doses to form an insoluble compound, copper phosphide. Permanganate of potassium solution, one per mille, has been recently advised to oxidize the phosphorus, while peroxide of hydrogen solution is of less value. In the secondary stage alkalies are recommended in order to neutralize the excess of sarcolactic acid formed in the tissues.

Phosphorus necrosis has to be treated surgically on the same principles as other necroses of bone.

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XXX. ARSENIC.

Some of the less active preparations of arsenic, such as the sulphides, Realgar ($As_2''S_2''$) and Orpiment ($As_2''S_3$), have been known in therapeutics since the beginning of the Christian era, but this metal was brought into especial prominence in later times through the frequent use of the more dangerous oxides in criminal poisoning. Thus

[illegible]

In colors, preservatives, in H_2SO_4. Metallic As unabsorbable - ion of H_3AsO_3 or its anhydride As_2O_3 — in tissues as arsenites. H_3AsO_4 less poisonous As ion alone active, compounds with C (organic) are inactive unless changed to H_3AsO_3

the notorious Aqua Tofana of the sixteenth and seventeenth centuries owed its activity to the presence of arsenic, and various arsenical compounds have been used up to the last few years more largely than almost any other poison in suicide and homicide. This is to be explained by their having been widely employed in the arts, and thus being readily accessible to all, and by the general recognition of their poisonous nature. Of late years intentional arsenic poisoning has become somewhat less common, though on the other hand, accidental poisoning is still met with not infrequently, especially in the chronic forms. Many of these chronic cases are extremely difficult to diagnose, and probably often pass unrecognized by the attending physician. In view of this fact it seems desirable that more stringent measures should be taken to reduce the use of arsenic in the arts, and especially to prevent its being brought in contact with food. The danger of the use of the green arsenical dyes, such as Scheele's Green (arsenite of copper), and Schweinfurt's Green, or Paris Green (arsenite and acetate of copper), is now generally recognized, but arsenic is still used in the preparation of other colors, and these may give rise to poisoning from the imperfect removal of the metal. It has also been used in dilute solution to preserve food, and a solution is often sprayed upon grape vines and other plants to preserve them from the attacks of insects. Poisoning has occurred from these sources and is difficult to diagnose, as it is in some cases impossible to find the means by which the arsenic enters the system. A widespread epidemic of poisoning in England in 1900 drew attention to a source of arsenic which had not up to that time received the attention it merited. Several thousands of persons suffered from arsenic being contained in cheap beers made from glucose, in the manufacture of which sulphuric acid had been employed. The sulphuric acid was formed from iron pyrites containing arsenic, and the poison was carried from the sulphuric acid with the glucose into the beer. Sulphuric acid is used in the manufacture of so many drugs, foods and other substances in constant use, that this intimation that it may convey arsenic into articles where its existence has not hitherto been suspected, is of the gravest importance.

Metallic arsenic is insoluble in water, and passes through the alimentary canal for the most part unchanged and without action, but it is possible that small quantities may be oxidized to arsenious acid in the stomach and intestine under some conditions. Some symptoms have been observed when it is rubbed on the skin in a state of fine division, and these are probably due to its absorption in the form of an oxide. The characteristic "arsenic" action is induced by the salts of arsenious acid (AsO_3H_3), and by its anhydride (As_2O_3) which is often known as arsenic, and which exists in the tissues as arsenites. Arsenic action is therefore due, not to the element, but to the ion of arsenious acid. The anhydride and salts of arsenic acid (H_3AsO_4) cause similar symptoms, but are less poisonous and act

rsenious acid - sweet. After 1/2 hour. Can't swallow, abd pain + watery diarrhea (mucous, epith, blood) Anuria, dizziness, circ + resp weak; coma in 24 hrs - 2-4 days. 0.1 G fatal

more slowly than those of arsenious acid, and may probably owe their effects to the formation of arsenites in the tissues. The action being due to the ion and not to the element, it necessarily follows that compounds from which the ion is not liberated do not induce the arsenic action, or do so only when they are changed to bodies which can dissociate the arsenious acid ion. Thus organic arsenic combinations in which the metallic atom is directly attached to carbon are only feebly poisonous, but in course of time seem to be changed to arsenious acid in the tissues, and then cause typical poisoning.

Arsenious acid, which in the following pages will be taken as the representative of "arsenic" action, has a somewhat sweetish taste, and is therefore not so likely to be detected by the victim as many of the other poisons.

Symptoms.—In large quantities arsenic very often causes no symptoms for half an hour or more, but then the patient complains of a feeling of constriction in the throat, of difficulty in swallowing, and of discomfort in the stomach region. This soon increases to violent pain, and is accompanied by vomiting, and later by watery diarrhœa. The stools are at first of ordinary diarrhœic appearance, but later resemble the "rice-water" stools of cholera, in that they consist almost entirely of minute shreds of disintegrated mucous membrane suspended in a serous fluid; sometimes, however, they are clear and gelatinous in appearance. In some cases, blood appears in the vomited matter and also in the stools, but this is not by any means an invariable feature. The urine is diminished, or entirely suppressed, from the great amount of fluid eliminated by the stomach and bowel. These symptoms from the alimentary tract are accompanied by giddiness, cramps in the muscles, headache, and soon by collapse, with cold damp skin, pallor, feeble pulse and weak, sighing respiration; this later passes into coma, and death follows with or without convulsions. In cases in which the dose is smaller than the fatal one, or in which much of the poison is eliminated by vomiting, the patient may recover without further symptoms than those already described. Frequently, however, he recovers from the acute symptoms only to develop those of chronic arsenical poisoning. In some instances it is said that no symptoms are present except those of collapse and coma. In acute poisoning death may occur within 24 hours, but more frequently the patient lives for 2–4 days longer, and then succumbs to exhaustion. The fatal dose is very uncertain, because arsenic is very insoluble, and much of the poison may be thrown up by vomiting, or pass out in the stools unabsorbed. Thus in some cases, recovery has followed after very large quantities, while in others about 0.1 G. (1½ grs.) has proved fatal.

Chronic Arsenic Poisoning may arise from a single large dose, the effects persisting for weeks or months after the ingestion and new symptoms arising as the earlier ones disappear; more frequently, however, it is induced by the prolonged absorption of small quantities. The milder symptoms may arise from its therapeutic use, but typical

Chronic: vomit, lang., stomach heavy, weak. Then conjunctiva red, swollen, catarrh, jaundice, all sorts of eruptions & bronze pigment. Then local anaesthesia & loss of function, headache, loss of sensation proportion. esp leg | Pb - forearm of extremities, with atrophy

cases are generally due to the presence of arsenic in the form of dyes in wall paper or clothes, or in stuffed animals in the rooms inhabited by the victims, or to the constant handling of arsenical pigments and other compounds in mines and manufactories. Widespread poisoning has been observed from the use of wines containing arsenic at Hyeres in France, from milk diluted with arsenical water in London, and from beer in the Manchester district. In these last cases the arsenic was in solution, but it often seems to be inhaled in the form of fine dust, which falls from the walls or other objects. It has been suggested that the arsenic dyes are decomposed by microbes and the volatile arseniuretted hydrogen (AsH_3) inhaled, but there seems no reason to suppose that this is the case, and the inhalation of fine particles is a sufficient explanation.

The symptoms of chronic arsenic poisoning, which are often very obscure, may be divided into three phases. In the *first* of these, the patient complains of weakness and languor, loss of appetite, some nausea and occasionally vomiting, with a sense of heaviness and discomfort in the stomach. Diarrhœa may be present, but is often absent, and in fact some constipation may occur.

In the *second* phase the conjunctiva is often red and inflamed, and symptoms of coryza appear, with sneezing, hoarseness and coughing, from a catarrhal condition of the mucous membranes of the nose and larynx. Some swelling of the liver and jaundice may occur, but these are not generally well marked. Skin eruptions of various forms—papular, vesicular, or erythematous—are generally noted; very often the epidermis falls off in fine brownish scales, or, in the hands and feet, in large flakes (keratosis); a curious pigmentation is very common, the skin assuming a dark metallic color resembling in extreme forms that produced by rubbing a lead pencil upon it (arsenic melanosis). This pigmentation is much more marked in persons of dark complexion than in fair people, in whom it may be indistinguishable from ordinary freckles; it generally disappears when the patient is removed from the poisonous atmosphere, but has been permanent in some cases. In prolonged poisoning the eruptions may simulate almost any form of skin disease, and the hair and nails fall off. Herpes is not infrequently observed and points to nervous disturbances such as are prominent features in the next phase.

These phases are not always distinct in cases of poisoning, and very often some of the symptoms of the second phase may appear before any marked disorder of the digestive tract. In the prolonged therapeutic use of arsenic, the first indications of commencing poisoning are redness, suffusion and swelling of the conjunctiva and eyelids, and dryness of the nose and throat, as in coryza. On the other hand, in workmen exposed to arsenical dust, the first symptoms may arise from the skin or from bronchial irritation.

The *third phase* is marked by disturbance of sensation and motion in localized areas, generally in the hands and feet (peripheral neuritis). It is often ushered in by intense persistent headache or by acute pain located around the knee, ankle or foot, less frequently in the wrist and hand. The patient complains of formication in the extremities, and of the discomfort caused by the pressure of the bedclothes on the feet and legs. The palms of the hands and the soles of the feet are often red, swollen and extremely sensitive to touch (erythromelalgia), and pressure on the muscles induces the most intense pain. Later, sensory paralysis may set in, especially in the extremities, and the less acute sense of touch in the feet and hands induces symptoms resembling those of locomotor ataxia. The sensitiveness to heat and cold may be exaggerated or dulled, or sometimes heat is not appreciated, while cold causes intense pain. The sense of pain varies in different cases, in some being abnormally acute, in others deadened. These sensory disturbances are followed in severe poisoning by motor paralysis, which generally appears in the extensor muscles of the toes, later in the peronei muscles. More rarely the flexor muscles of the leg and foot are involved, and in some cases the affection commences in the extensors of the hand and fingers. As a general rule the paralysis is confined to the extremities, but in some cases it has been found to invade the trunk. It is generally, but not invariably, symmetrical, and the muscles affected atrophy rapidly, and contract weakly to the galvanic shock, not at all to the faradic except in the beginning of the affection. This lessened excitability of the muscles sometimes appears before the typical degeneration reaction is observed but is then followed by it later. The muscles are abnormally excitable to mechanical stimulation, however, while the tendon reflexes are generally entirely absent. There is sometimes some difficulty experienced in diagnosing arsenic from lead paralysis, but in the former there is often a history of acute poisoning, while the latter is almost invariably due to prolonged absorption. Disturbances of sensation are much more common in arsenic than in lead palsy, and in the latter the forearm muscles are generally affected first, in the former those of the leg. In arsenic poisoning atrophy is said to occur much more rapidly, and there is no line on the gums. Another condition which presents still greater difficulties in diagnosis is alcoholic neuritis. But in the latter skin eruptions are extremely rare, coryza is not present, and there are generally more marked brain symptoms than in arsenical cases. In doubtful cases the urine and the hair of the patient should be tested for arsenic.

Arsenic paralysis may appear as early as three days after an acute intoxication, but is commonly observed later, and may occur only after 3–4 weeks. Some authors have asserted that in chronic arsenic poisoning there is a paralysis of the sexual powers (anaphrodisia), and ascribe this to an action on the nerves of the sexual organs, similar to that observed in the extremities, but this symptom is not by any means generally present, and, in fact, abnormal sexual excitement has been noted in some cases.

In very prolonged arsenic poisoning the patient may sink into an apathetic, semi-idiotic condition, or may become epileptic. In most

G.I. no sym of acid corrosion, but is fatty degen, swollen + congested + action in vessels.

cases the symptoms slowly disappear when the poison is removed, but even slight paralysis may last for many years before it is entirely cured, and after complete degeneration of the muscles little improvement is to be expected. The contractures which follow are generally due to the unopposed action of the sound muscles, but sometimes arise from the shortening of the paralyzed ones.

Arsenic poisoning generally occurs from the inhalation of particles of the drug, or from swallowing solutions or powders. But the same symptoms have been elicited in animals by subcutaneous or intravenous injection, and some cases of poisoning in man are recorded in which the arsenic gained entrance to the body through its application to burns or other surfaces denuded of skin, or from its application to mucous membranes, as in the vagina.

Action.—The symptoms of arsenic poisoning, as far as the **Alimentary Canal** is concerned, resemble those of corrosive poisoning so closely that it was long supposed that arsenic had some destructive effect upon albumins, resembling that of the acids and corrosive metals. Many attempts to form a combination between proteins and arsenic have been made, but have proved fruitless; arsenites and arsenious acid do not coagulate proteins or change them in any way, except when applied in such enormous quantities as never reach the stomach.

The action of arsenic on the alimentary canal cannot be explained as due to any ordinary form of corrosion, therefore, although the symptoms and the post-mortem appearances resemble in many points those of the corrosive poisons. Thus the mucous membrane of the stomach is generally found red and swollen, either in patches or throughout its whole extent. Hæmorrhages into it are occasionally present, but are not by any means a constant feature. The epithelial coat can be rubbed off very easily, and is found to be in a state of fatty degeneration, and sometimes resembles a false membrane. Where arsenic has been swallowed in powder, and has remained in contact with the wall for some time, the congestion is often marked, and here even erosion may appear. In some cases no congestion of the stomach is met, the only lesion consisting in cloudy swelling and fatty degeneration of the gland-cells, similar to that mentioned under phosphorus.

The intestine presents very similar appearances, the mucous membrane being swollen and congested, more especially around Peyer's patches. It contains a quantity of thin fluid with flakes of membrane, resembling exactly the rice-water stools of cholera, and in fact it may be difficult to distinguish the intestine of arsenic poisoning from that of cholera. Small particles of arsenic are often found in the stomach and bowel, even after profuse vomiting and purging. In some cases the redness and congestion extends up to the throat and causes a feeling of soreness in the mouth.

This action of arsenic on the alimentary tract is not due to corrosion simply, for the same symptoms arise when arsenic is absorbed from the subcutaneous tissue, or from the broken skin, though only traces

Watery stools due to vessels dilatation fatty degen. due to specific to action in g.i. tract. In therapeutic doses it increase metabolism + appetite

of arsenic are found in the contents of the stomach and intestine when it is injected in this way. Besides, arsenic does not change proteins in solution as the corrosive poisons do, and cannot therefore elicit typical corrosion. Boehm and his pupils have suggested that the gastro-intestinal action of arsenic is due, not to any direct action on the epithelium, but to the vascular changes induced by it. They suppose that the extreme dilatation of the intestinal vessels and capillaries gives rise to the congestion and swelling, and this in turn to the destruction of the lining membrane, perhaps by the exudation of fluid beneath the epithelium. This transudation of fluid is certainly in accord with the watery character of the stools in arsenic poisoning, but the explanation does not seem entirely satisfactory, for it fails to account for the fatty degeneration and the cloudy swelling of the epithelium, which are in some cases the only lesions found here. The fatty degeneration is not confined to the stomach and bowel, but involves a number of other organs, although it is not as a general rule so widely distributed as in phosphorus poisoning. Arsenic then must be considered to have a specific action in causing fatty degeneration of the epithelium of the stomach and intestine. This in itself is sufficient to explain many of the symptoms from these organs, although it may well be that the vascular action is the cause of the excess of fluid in the intestine, and in fact, the fatty degeneration alone is insufficient to explain this feature, which is absent in phosphorus poisoning. In cases of poisoning where the arsenic is taken by the mouth, and especially when large quantities of dry arsenious acid are swallowed, the specific action on the epithelium and the vascular action are probably intensified by the direct contact of the poison.

In therapeutic doses arsenic is said to increase the appetite and promote digestion, an effect which may perhaps be due to the specific action on the epithelium, this in its milder forms proving of advantage to the organ, though in excess it leads to its degeneration.

The action of arsenic on the **Circulation** has been investigated by several authors, who have obtained discordant results. In the frog the heart is slow and weak, eventually becomes irregular, and ceases in diastole after comparatively small doses; the action seems to be a direct paralysis of the muscle. In the mammal the heart is little affected by arsenic, but a very marked fall of the blood pressure follows the injection of large doses intravenously. This is due to dilatation of the arterioles and capillaries from a direct action on the muscular coat; the vessels of the splanchnic area seem more susceptible to this arsenic action than those of the rest of the body. The dilatation of the mesenteric vessels leads to very marked congestion of the stomach and bowel, and reduces the blood-pressure to zero. Some evidence has been brought forward that under arsenic the capillaries permit the passage of fluid into the tissues more readily than normally; this may explain the appearance of œdema in cases of poisoning and also the large amount of fluid in the stools and vomited matter.

In chronic – peripheral neuritis. In acute, C.N.S. failure due to G.I. loss of fluid etc. Cord + brain affected directly, perhaps. No effect on skin unless long, then pustules = eruptions. Not corrosive as alkalies + acids (ppt proteins). Subcutaneous O.K. On raw surfaces + m.m. it destroys deeply

The **Respiration** is somewhat accelerated at first by the intravenous injection of small quantities of arsenic, but afterwards returns to its normal rhythm. In cases of poisoning in man the respiration does not seem to be much affected until late, but it ceases before the heart, probably from the exhaustion and low blood-pressure, and not from any specific action on the centre.

The action of arsenic on the **Central Nervous System** has been repeatedly examined. A descending paralysis is elicited in the frog, the animal first losing its spontaneous movements, and then its reflexes, and the terminations of the motor nerves being involved only very late in the intoxication. There is no question that the brain, spinal cord and nerve ends are directly acted on in these animals, for paralysis is elicited by arsenic much sooner than by arrest of the circulation by excision of the heart. In mammals there are generally no certain indications of direct action on the nervous system in acute poisoning, for the weakness and prostration, and the final loss of consciousness and coma may be attributed to the exhaustion from the gastro-intestinal effects rather than to the centres being immediately affected.

The pathology of the nervous disturbances observed in chronic poisoning, and often after a single large but not immediately fatal dose, bears no relation to the effects observed in animals in acute poisoning. The symptoms in chronic poisoning all point to peripheral neuritis as the cause, and the characteristic lesions in the nerve trunks have been shown to occur both in man and animals exposed to the prolonged action of arsenic. In severe cases the spinal cord may also be involved secondarily. The peripheral muscles and nerves are little affected in acute poisoning.

The unbroken **Skin** is not affected by arsenic, unless when it is applied repeatedly or allowed to remain in contact with it for some time, when it may give rise to redness, pustules or vesicles and later to violent erysipelatoid inflammation. It has not, however, any such corrosive action on the skin as is possessed by strong acids, and the subcutaneous injection of arsenic is not painful. It is more active when applied to denuded surfaces and to the mucous membranes, destroying them to some depth and causing acute pain, but even here it acts more slowly than ordinary caustics. It seems to act only upon living cells, and unlike acids and alkalies, forms no combinations with the dead tissues. The local effects of arsenic on the skin are seen only in workmen handling arsenic, as in color factories, in which affections of the skin of the face, hands and scrotum are by no means rare.

In arsenic poisoning skin eruptions are common, and may be due in part to circulatory disorders, but are to be ascribed for the most part to the direct action of the drug on the skin. This appears to accelerate the growth and proliferation of the epithelium, which is found to be increased in thickness, but which in very severe cases shows signs of atrophy and degeneration. Arsenic has been found in appreciable amount in the hair and epidermal scales, and in the fluid

As on [illegible]. In skin. May cause epidermal hyperplasia. In single doses increase reds & bone marrow hyperemia. In large doses metab. catabolism increased - NH3 esp as cb. catabolism stops at lactic acid stage. Glycogen [illegible] not [illegible] liver

of a blister in patients treated with it, and changes in the condition of the skin in animals have also been observed. Thus Ringer found the epidermis of the frog peel off with great ease when it was poisoned with arsenic, and Nunn ascribes this to the softening of the protoplasm of the deeper cells of the epidermis; analogous changes have been observed in the cornea.

The melanosis of arsenic poisoning seems to be due to the deposition not of an arsenical compound, but of some organic product in the deeper layers of the corium. The symptoms of irritation of the mucous membranes of the eye, nose and larynx are analogous to the skin eruptions.

The action of arsenic on **The Blood** is still obscure, although it is frequently prescribed in various forms of anæmia. In chlorosis and in normal persons, it is said to diminish the number of the red corpuscles, but not to alter the total hæmoglobin of the blood. Stockman and Greig found the blood cells and hæmoglobin unaltered by arsenic in normal animals, but describe the bone-marrow as evidently in a state of unusual activity, indicated by its increased vascularity, greater number of red blood corpuscles and lessened fat cells. In a case of pernicious anæmia recently examined by Engel, it was found that arsenic increased the number of young newly formed red cells while the number of more mature corpuscles was diminished. Bettman states that in subacute poisoning in rabbits, the red cells and hæmoglobin are diminished, and nucleated red cells appear in the blood in some number; he holds that arsenic acts on the blood, and also on the blood-forming organs. After hæmorrhage the blood is said to regenerate more quickly if arsenic is given, and the number of red cells rises faster than the hæmoglobin.

In some cases of arsenic poisoning **Fever** is observed; this does not seem due to any specific action of the drug, but to the inflammation of the mucous membranes and the skin.

The **Metabolism** is affected by a poisonous dose of arsenic in the same way as by phosphorus, but the alteration is not generally so marked and is liable to be overlooked, owing to the more intense action on the alimentary canal. The nitrogen of the urine is considerably greater than that of inanition, but it is not quite clear whether this is due to an increase in the urea or to other nitrogenous substances. The ammonia is probably augmented, for a considerable amount of lactic acid has been obtained from the urine, and the alkalinity of the blood is reduced owing to the formation of this acid in excess. The glycogen of the liver disappears entirely, and the liver seems incapable of forming it from the sugar of the food. Lesion of the medulla oblongata (diabetes puncture) does not cause glycosuria after arsenic, but curara and other drugs are still capable of eliciting this symptom. The fatty degeneration of the epithelium of the stomach and intestine has been mentioned already, but this alteration is not confined to these tissues, being found in the liver and kidney, in the muscle cells of the heart, blood vessels and striated muscles,

Jaundice – bile pigments & acids in the urine
" more marked in P poison.
Growth & nutrition improved.

and in the lining epithelium of the alveoli of the lungs. Small necrotic foci have been observed by Wolkow in the liver, along with signs of active division of the parenchymatous cells, as in phosphorus poisoning.

The changes in the metabolism under arsenic resemble those under phosphorus, so that they have generally been regarded as arising from a similar action. But it is found that while phosphorus accelerates autolysis outside the body, arsenic tends to delay it. And the livers of animals poisoned with arsenic appear to contain less of the decomposition products of proteins than normal. The resemblance is so close, however, in other respects that it seems possible that these divergences may be susceptible of explanation.

The metabolism is less affected by arsenic than by phosphorus, for the fatty degeneration is less marked and less lactic acid is excreted. Nencki and Sieber have also shown that benzol can be oxidized to phenol in animals poisoned with arsenic, while in phosphorus poisoning the tissues are unable to effect this.

The fatty degeneration may have the same results as in phosphorus poisoning. The liver is somewhat enlarged and the pressure on the bile ducts prevents the escape of bile into the intestine, and thus induces jaundice and the appearance of bile pigments and bile acid in the urine. Jaundice is seldom, however, a very marked feature in arsenic poisoning, and is often entirely absent. The bile is said to contain albumin, red blood cells, and casts as in phosphorus poisoning, but does not present other changes except immediately before death.

The prolonged administration of arsenic in quantities insufficient to produce chronic poisoning is reputed to have some effect on the **Growth and Nutrition.** It is difficult to obtain accurate data in regard to this point, and while the improvement in nutrition is attested by a number of independent observers, other equally careful investigators have not been able to confirm their results. Gies treated some of a litter of young rabbits with arsenic in minute doses for several weeks, and found that they weighed more, and were larger in every way than the untreated animals; the subcutaneous fat was much greater in amount, the bones were longer, and the muscles more developed. The long bones presented the appearance described by Wegner under phosphorus treatment, being longer and containing more dense bone both in the shaft and the epiphyses. Female rabbits treated with arsenic bore young of abnormal size and weight. Several other observers have described a more rapid growth and greater activity in young animals treated with arsenic, and an increase in weight is often noted in man. On the other hand Stockman and Greig observed no change in the growth of animals under prolonged treatment with arsenic, and found that the only tissues affected were the growing bones, which appeared denser than usual.

The improvement in nutrition has not been explained, though a slight decrease in the nitrogenous excretion and in the amount of nitrogen in the stools has been noted by Weiske, who holds that more

[illegible]
absorb. ancy + it passes out in stools. rather than in urine. No tolerance
when inhaled or injected.

of the food is utilized by the digestive apparatus, and at the same time, less protein is decomposed in the tissues. The change in the amount of nitrogen excreted is so small, however, that doubt may be entertained whether it may not be due to unavoidable errors in the estimation, and other investigators have been unable to detect any alteration attributable to the drug. Fresh investigation of this point is thus required before certainty can be reached regarding the effects on the nutrition, and still more regarding the explanation of the alterations.

When small quantities of arsenic are taken habitually, **Tolerance** is established, and the dose may be gradually increased until it far exceeds that which would be poisonous in ordinary persons. This is the explanation of arsenic-eating which is known to exist in different parts of the world, but which is most widespread and best known in Styria and the Tyrol. The peasants there indulge in the poison habitually, and believe that it enables them to work better, and in particular to climb the mountains with less effort and less respiratory distress. They also credit it with improving their complexions and general appearance, and give it to their horses in order to render their coats more smooth and glossy, and to make them stronger and fatter. Who's Who Knapp administered 0.4 G. (7 grs.) of arsenious acid to one of the peasants at Graz without inducing any effects whatsoever. Arsenic has also been isolated from the urine of arsenic eaters, showing that some of the drug is absorbed. Arsenic-eating is said to be indulged in to a considerable extent by young women in some countries with the object of improving the complexion and figure, and cases of arsenic habit have been described in different parts of America and elsewhere. As far as can be observed the habit is not deleterious, for the Styrian peasants live to old age, and no symptoms attributable to the poison have been noted. As a general rule large doses are taken once or twice a week, and no fluid is swallowed for some time afterwards.

Cloetta treated animals in this way with dry arsenic and succeeded in obtaining tolerance of large doses; at first a considerable proportion was absorbed and excreted in the urine, but as the treatment continued, less appeared in the urine and more in the stools. An animal that was not injured by large quantities given by the mouth, succumbed to quite small doses administered hypodermically. He holds that the tolerance to arsenic arises from the absorption from the intestine decreasing on prolonged use. No tolerance is attained when arsenic is injected hypodermically.

As a contrast to the Styrian peasants, the miners of Reichenstein may be mentioned, who are constantly exposed to arsenic owing to its being contained in large quantities in the ore. These people are described by Geyer as shortlived, very subject in childhood to severe rickets and in adult life to dropsies and respiratory diseases; they offer little resistance to microbial infection and frequently present the skin and nervous symptoms of arsenic poisoning. Here the arsenic is

As held tenaciously by tissues. Eliminated by urine, much by hair
+ epidermis + milk esp. liver, kid, spleen, [illegible] intest

probably absorbed from the respiratory tract and not from the bowel, and this would account for no tolerance being acquired if Cloetta's view is correct. Differences in general nutrition may also play a part, for Delepine and others have found that animals supplied with abundant food and in good hygienic conditions survive under chronic arsenic poisoning much longer than less well nourished ones. This difference in the nutrition may also explain the fact that in epidemic poisoning, as in the Manchester cases, comparatively few of the persons exposed to the poison exhibited any symptoms from it.

Arsenic is **Excreted** very slowly, some appearing in the urine and fæces within 24 hours, but only about one-fifth of that absorbed being eliminated in this way. The rest is stored in the tissues for a long time and slowly got rid of in the hair and epidermis, in which arsenic may be found for many months after it has disappeared from the urine and fæces. Traces may be found in other secretions, and fatal intoxication has been observed in a child from the milk of its mother, who was suffering from acute poisoning. In the urine arsenic appears in part in organic combinations. It is probable that the effects, especially the paralysis, last long after the drug has been excreted, lesions having been induced which are only slowly recovered from.

Arsenic disappears rapidly from the blood when injected, being taken up by the tissues in which it forms firm combinations with the nucleins; it is found chiefly in the liver, and is also deposited in the kidney, in the walls of the stomach and intestine, and in the spleen and lungs. Much smaller quantities are found in the muscles and in the nervous tissues, in which it is said to occur in larger proportion in the white than in the gray matter. It has been detected in the cancellous bones of the skull and vertebræ, after it had disappeared from all the other organs.

Arsenic is poisonous to many of the lower forms of life, as well as to the vertebrates; thus it has been found that its presence in comparatively dilute solution (one part of arsenious acid in 30,000 parts of water) hinders the development of, and eventually kills algæ and the seeds of the higher plants. On the other hand, moulds grow abundantly in a solution of potassium arsenite (1 per cent.) containing some organic matter, and the alcoholic fermentation proceeds in the presence of arsenic, although it is somewhat retarded at first; very dilute solutions of arsenic even accelerate the fermentation, as is true of most other antiseptics. Arsenious acid is only about one-tenth as strong an antiseptic as perchloride of mercury, and the spores of anthrax are destroyed only after ten days in a one per mille solution. It has therefore a greater antiseptic power than many of the other acids, but compared with its action on the higher forms of life, it is but slightly poisonous to the fungi. It seems to have no effect on the activity of the ferments, such as pepsin, myrosin and emulsin. Some pathogenic protozoa are extraordinarily susceptible to the action of arsenic; thus a concentration of arsenic in the blood of 1 in 200,000 is sufficient to destroy many of the trypanosomes, while other protozoa living in water may survive in a 1 in 5,000 solution. All the parasitic protozoa are not so readily destroyed, however, for that of malaria is found to be much more resistant. When an animal infected with trypanosomes is treated with arsenic, the parasites often disappear from the blood for some days or weeks and then reappear, but can again be expelled by

trypanosomes [illegible] – ie they develop resistance. See Richards' notes on 606 + neosalvarsan
As effects on m.m. & skin & circ. Ph = fatty degeneration.

arsenic, though for a shorter time, the trypanosomes surviving having developed a certain resistance to the action of arsenic. This insusceptibility to arsenic is inherited by their descendants if a new animal is infected from the first one, and arsenic-resistant generations may be propagated through many hosts. The same process occurs when trypanosomiasis is treated with other remedies; in course of time a resistant race of parasites is generated. But a strain that is resistant to arsenic is susceptible to these other remedies, and *vice versa* a race resistant to trypan-red is susceptible to arsenic.

The arsenates are much less harmful to lowly organized forms, for seeds and algæ as well as moulds grow in a neutral solution abundantly, and even the infusoria do not seem injured by it to any marked degree. Apparently these plants and animals are incapable of reducing it to arsenious acid, and are therefore not more affected by it than by other acids.

The bodies of persons poisoned with arsenic are said to remain undecomposed for a remarkably long time, and to tend to become mummified. The statement is still disputed, but is vouched for by a number of authorities. It is certainly not invariably the case, and little weight is to be laid upon mummification in determining whether arsenic poisoning was the cause of death in exhumed persons.

No account of the pharmacology of arsenic would be complete without mention of the theory advanced by Binz and Schulz to explain its action. They suppose that arsenious acid is oxidized to arsenic acid by the living tissues, and the arsenic acid again reduced to arsenious. In this way oxygen is alternately withdrawn from and supplied to the protoplasm, and this alternate reduction and oxidation they suppose to be the essential feature of the action of arsenic. The grounds on which this explanation is based must be sought in the numerous papers on the subject by these authors, and it may suffice here to state that while arsenic acid appears to be reduced and arsenious acid oxidized in the tissues, these processes are probably only gradual. Otherwise it would be difficult to explain how arsenious acid is so much more poisonous than arsenic acid, for if the latter were readily reduced to arsenious acid it would be equally toxic.

Arsenic and phosphorus are included in one group in chemistry, and their effects on living organisms present sufficient resemblance to justify their association in the pharmacological system. The mucous membranes and the skin are more affected by arsenic, however, and the circulation is more rapidly depressed, while the fatty degeneration of the protoplasm of the vertebrates is much more prominent in phosphorus poisoning. The differences between their effects are more in degree than in kind, and there seems no question that their ultimate action on protoplasm is of the same nature. It is to be noted, however, that there is no reason to suppose that phosphorus owes its action to any of its numerous compounds with oxygen, while it is probable that the oxides of arsenic alone are capable of modifying vital functions.

The **Sulphur Compounds** of arsenic are entirely insoluble and are therefore not absorbed as such, but it seems likely that small quantities of arsenious acid are formed from them in the intestine by microbes. Commercial orpiment often contains large amounts of arsenious acid.

Arseniuretted Hydrogen (AsH_3) is an exceedingly poisonous gas, which has caused a number of fatal accidents from being inhaled accidentally in chemical laboratories. One source of danger is the liberation of hydrogen from acids by the action of zinc, which often contains arsenic and therefore gives rise to this gas. It differs entirely from the oxides of arsenic in its

S As comp used but probably some changed to the oxide. AsH_3 a poison
Some Na cacodylate → inorganic As. Atoxyl - action on trypanosomes
probably due to action of inorganic As - may cause blindness - not so As itself [illegible]

action, and there is no reason to suppose that it forms these in the body. Possibly traces of arseniuretted hydrogen are formed from arsenious acid in the intestine, but in insufficient quantities to have any appreciable effect. Arseniuretted hydrogen acts as a molecule, AsH_3, arsenites as ions, and the fact that both molecule and ion contain an atom of arsenic does not necessarily entail that their effects shall bear any resemblance.

Arseniuretted hydrogen acts by destroying the red corpuscles of the blood, and induces intense headache, nausea and vomiting, prostration and fainting fits, cyanosis and collapse. Hæmoglobin, methæmoglobin, hæmatin and occasionally blood are passed in the urine, and more rarely the stools contain blood. Sometimes the urine is entirely suppressed from the tubules being plugged with blood cells and débris, and intense icterus appears from the formation of excess of bile pigment from the hæmoglobin of the disintegrated corpuscles. Œdema of the lungs or sudden failure of the heart is the cause of death. Some of the gas is excreted by the lungs, and may be recognized by its garlic odor, and some arsenic appears in the urine, but it is not known in what form.

AsH_3 [illegible]

A number of **Organic Arsenic Compounds** have been used in therapeutics. The earliest of these was *sodium cacodylate* ($((CH_3)_2AsOONa)$), which is relatively feeble in action, as it does not release the arsenious ion except in very small amounts in the tissues. Most of the cacodylate is thus eliminated unchanged in the urine, some may be reduced to the cacodyl oxide and excreted in this form, while a small proportion is apparently changed to the inorganic form and exercises the typical arsenic action. The amount which undergoes this transmutation is unknown and probably varies so that cacodylate is not practically useful. *Arrhenal* ($(CH_3As(ONa)_2)$) resembles the cacodylate in action.

Atoxyl, or sodium arsanilate ($(NH_2C_6H_4OAs{<}{}^{ONa}_{OH})$) has recently been used extensively in trypanosome infections, in which it seems to present some advantages over the inorganic arsenic salts. It is absorbed rapidly and circulates in the blood longer than the arsenites, which are taken up by the tissues rapidly and thus can exert only a transient action on parasites living in the plasma. Atoxyl is excreted in the urine for the most part unchanged, but a small proportion undergoes decomposition and is believed to liberate the arsenious ions. Trypanosomes are not affected by atoxyl outside the body more than by many other substances, and there has been some discussion as to how its specific action arises in the body. Ehrlich holds that it is partially reduced in the tissues and that the product of reduction is the active trypanocide, and he has shown that such reduced bodies act very powerfully on trypanosomes in test-tube experiments; on the other hand, it has not been proved that this reduction occurs in the tissues. Others believe that the inorganic arsenic formed from atoxyl is the active agent, and there is no question that inorganic arsenic destroys the parasites both in the blood and in the test-tube; the more powerful action of the small quantities of arsenic liberated from atoxyl in the body may perhaps be explained by its being freed in the blood or in the interior of the parasite into which the atoxyl has penetrated, while inorganic arsenic leaves the blood very rapidly. Strong evidence in favor of the view that atoxyl acts in virtue of its liberating arsenic is offered by the observation that trypanosomes which have become resistant to atoxyl have also a low susceptibility to arsenic. In a number of cases atoxyl has given rise to poisoning in man, the symptoms being dryness of the throat, headache, giddiness, fever, colic, vomiting and diarrhœa, nephritis and paresis of the lower limbs; the most serious effects, however, are disturbance of vision, which may advance to total and permanent blindness. In animals ataxia and tremors are seen, especially in the cat, and renal hæmorrhages in the dog. Blindness has also been induced experimentally in animals, and is found to

As, O, - [illegible]

arise from degeneration of the ganglion cells of the retina and of the fibres of the optic nerve. These symptoms are not those ordinarily induced by arsenic in chronic poisoning, and it has been suggested that the aniline component is responsible for them, but this does not seem probable; and they often supervene after atoxyl has been discontinued, so that it seems improbable that this substance, which is so rapidly eliminated, is itself the agent. It seems possible that these symptoms are again the result of the arsenic liberated from the atoxyl, and that they are different from those ordinarily seen under arsenic, because the arsenic is liberated in unusual parts of the body, owing to the atoxyl penetrating where the inorganic forms fail to reach.

PREPARATIONS.

ARSENI TRIOXIDUM (U. S. P.), ACIDUM ARSENIOSUM (B. P.) (As_2O_3), arsenous or arsenious acid anhydride, white arsenic, ratsbane, forms a white powder, or opaque, porcelain-like masses, or a transparent, amorphous surface like glass. It dissolves slowly in cold water, the glassy variety requiring about thirty, the porcelain about eighty parts of water. It is almost tasteless and has no odor. 1–5 mgs. ($\frac{1}{60}$–$\frac{1}{12}$ gr.), in pill or solution, after meals. The "Asiatic" pill consists of arsenic, black pepper and liquorice.

✓ *Liquor Acidi Arsenosi* (U. S. P.), *Liquor Arsenici Hydrochloricus* (B. P.), a one per cent. solution of arsenous acid acidulated with hydrochloric acid. 0.05–0.5 c.c. (1–8 mins.), 3–5 drops three times daily, after meals.

[illegible] ✓ LIQUOR POTASSII ARSENITIS (U. S. P.), LIQUOR ARSENICALIS (B. P.), Fowler's solution, contains one per cent. of arsenous acid neutralized with .05-.5cc bicarbonate of potash, to which compound tincture of lavender is added to give color and flavor. 0.05–0.5 c.c. (1–8 mins.), 3–5 drops three times daily, after meals.

Sodii Arsenas (U. S. P.) ($Na_2HAsO_4 + 7H_2O$) forms colorless, odorless crystals, very soluble in water, with a mild, alkaline taste. 1–5 mgs. ($\frac{1}{60}$–$\frac{1}{12}$ gr.).

Sodii Arsenas (B. P.), *Sodii Arsenas Exsiccatus* (U. S. P.) (Na_2HAsO_4), is prepared from the ordinary arsenate (U. S. P.) by driving off the water of crystallization, and forms a white powder. $\frac{1}{40}$–$\frac{1}{10}$ gr.

Liquor Sodii Arsenatis (U. S. P., B. P.), Pearson's solution, a one per cent. solution of the sodium arsenate of the respective pharmacopœias. 0.05–0.5 c.c. (1–8 mins.).

Arseni Iodidum (U. S. P.), *Arsenii Iodidum* (B. P.) (AsI_3), glossy, orange-red crystals with an iodine odor and slowly giving off iodine in the air; it is soluble in 7 parts of water, but the solution soon decomposes into arsenous and hydriodic acids. 3–10 mgs. ($\frac{1}{20}$–$\frac{1}{6}$ gr.).

✓ LIQUOR ARSENI (ARSENII, B. P.) ET HYDRARGYRI IODIDI (U. S. P., B. P.), Donovan's solution, contains one per cent. of arsenic iodide and one per cent. .05-.5 of red mercuric iodide. This solution is clear and yellowish, without odor, but with a harsh metallic taste. 0.05–0.5 c.c. (1–8 mins.), after meals.

Some mineral waters contain arsenic, that of Levico as much as 8 mgs. per litre.

Atoxyl, sodium arsanilate ($C_6H_7NAsO_3Na$), is a white crystalline powder containing 27.2 per cent. of arsenic metal, soluble in six parts of water or about 125 parts of alcohol. It has a faint saline taste. Dose hypodermically, 0.1–0.3 G. (1½–5 grs.) per day in 10 per cent. solution.

A number of other arsenic compounds similar to atoxyl have been tested recently in trypanosomiasis and other diseases. Of these *Soamine* is practically identical with atoxyl, differing only in the amount of water of crystallization. *Arsacetin* is acetyl-atoxyl (CH_3CO—$NHC_6H_4OAsOHONa$), and resembles the parent substance closely in effects. *Arsenophenylglycin* is stated by Ehrlich to be superior to atoxyl, but has not yet received adequate examination.

Sleeping sickness, malaria, rheumatism? neuralgia. Appetite up in weakness, cachexia & apathy - In chronic skin diseases

Therapeutic Uses.—The action of arsenic as ascertained from experiments on the lower animals and from cases of poisoning in man throws little light on its use in therapeutics, and so little is known of the pathology of most of the conditions in which it is found of benefit, that no attempt can be made to bring the two series of observations into relation. The treatment of trypanosoma infections, such as sleeping sickness, with arsenic and its compounds has given rise to the idea that many of the conditions in which arsenic is useful may arise from protozoal infection. But there is no question that arsenic acts in other ways than by destroying parasites, and such speculation is futile until the cause of these diseases has been determined.

Arsenious acid has been used externally as a caustic, formerly in various forms of malignant disease, more recently in lupus, in which it is said to destroy the diseased surface while leaving the healthy skin unaffected. It has been superseded, however, by the introduction of surgical measures, such as scraping with the sharp spoon. Arsenic in substance is still used in dentistry to destroy the pulp in decayed teeth.

Internally arsenic is used in malarial disease, especially in inveterate cases in which there is much cachexia. In acute cases it is also of benefit, but is much less certain in its effects than quinine, and it is very questionable whether it acts on the malarial organism, for its efficacy often seems due rather to its improving the general nutrition and lessening the cachexia and wasting. Many authorities, in fact, deprecate the use of arsenic in acute malaria, and would limit its use to the cachexia of old disease, while others advise its use with iron in ordinary cases, after the acute stage has been successfully treated with quinine.

Arsenic has also been used with benefit in neuralgia, especially when it assumes a periodic character, and in chronic rheumatism, but in many cases no definite improvement follows, and the conditions under which it is of value cannot be more accurately defined at the present time. Old cases of chorea often improve under arsenic, which may imply some action on the central nervous system, although, as has been stated, little alteration in the nervous functions is observed in animals except under very large doses. Asthma has also been treated with arsenic given by the stomach, or by the inhalation of arsenic from smoking cigarettes made with arsenical paper.

Small doses of arsenic are often of service in increasing the appetite and improving the general condition in diseases accompanied by cachexia, want of appetite, general weakness and apathy.

In pernicious anæmia, arsenic is said to be beneficial, but the improvement is only temporary. Many forms of skin disease are treated with arsenic, some of them with the happiest results. Thus in psoriasis, chronic eczema, and lichen ruber, marked improvement or complete recovery often dates from the beginning of the arsenic treatment. It is generally advised only in the chronic forms, and is said to be positively deleterious during the earlier stages of rapid cell proliferation.

[illegible] lymphoma [illegible]. Fowler's sol. after meals. Contraind: upset GI & fever except malaria! See below for sympt. — ~~appetite + stomach throat~~ + conjunctiva
Gastric lavage + emesis. [illegible] from mag oxide. Or Magnesia

then symptomatic treatment.

In lymphoma arsenic has been given internally and also by direct injection into the tumors, and often, though not by any means invariably, proves of value. Various other forms of leucæmia have been treated with less success.

Arsenic has been used in some forms of trypanosoma infection in animals, and has been found to improve similar conditions in man. The ordinary preparations are less often used than atoxyl and related substances, but the trypanosomes show less tendency to become resistant to the inorganic forms and it is now recommended that these diseases should be treated by both inorganic and organic compounds. Arsenic and atoxyl are undoubtedly of great benefit in these diseases, relieving the symptoms and prolonging life even in those cases in which they do not actually cure the infection. The specific effect of arsenic in trypanosomiasis has suggested that its action in malaria may be due to its destroying the parasite. And similar considerations have led to the treatment of syphilis with atoxyl in the hope that it might exterminate the parasite here also. It has proved of value in this disease, but is not to be compared with mercury and iodide in efficacy, and its use is only indicated in cases where these fail or for any reason are inadmissible.

Arsenic is in the great majority of cases prescribed in the form of Fowler's solution. It is generally advisable to commence with small doses, and to increase them as tolerance is developed, but some authorities advise large doses from the outset. Arsenic is always prescribed to be taken after meals, in order to avoid any possible action on the digestion. Several authors have recommended the hypodermic injection of Fowler's solution diluted with two parts of water. (Dose 0.5 c.c., 8 mins.) Arsenic is contraindicated in cases of irritation of the stomach and bowel, and is generally avoided during acute fever, except in malaria.

If symptoms of chronic poisoning begin to assert themselves, the drug must be discontinued at once. The first symptoms are generally disordered digestion, loss of appetite and discomfort in the stomach region, a feeling of constriction in the throat and redness and swelling of the conjunctiva and eyelids.

In Acute Arsenic Poisoning the stomach ought to be emptied at once by means of the stomach tube or by an emetic (apomorphine). The stomach washing is to be continued for some time, as arsenic is very insoluble. Iron or magnesium preparations have been advised in order to form a loose chemical combination with the arsenic; freshly precipitated iron hydrate formed by adding magnesia to a solution of iron sulphate forms the well-known arsenic antidote, or magnesia alone is sometimes given shaken up with water. Experiments on animals show these antidotes are useless and that reliance is to be placed on repeated and copious lavage only.

The collapse is treated by the ordinary measures, warmth and stimulants, such as caffeine and digitalis. In chronic poisoning, the paralysis is treated by stimulating the muscles with the galvanic current, the other symptoms by suitable general treatment.

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Metals alone non-toxic. Only when dissociable into the metal ion or oxide. Independent action of heavy metals: local, general. They ppt. proteins - forming insol salts, sol in excess of either [illegible]. These comp. ~~are~~ respond to metal reactions unless so firmly bound that they are masked.

PART IV.

THE HEAVY METALS.

HEAVY METALS.

A large number of important drugs, belonging to the chemical series of heavy metals resemble each other so closely in their action in living organisms that they may be readily grouped together in a division of the pharmacological system. Some authors include in this series arsenic and antimony, but the former presents so many analogies to phosphorus in its effect that it is preferable to treat it apart from the heavy metals. Antimony is certainly as closely related to arsenic as to this group, and may be regarded as a connecting link between them.

The metals as such do not induce any symptoms except from their mechanical properties. Thus mercury may be swallowed in large quantities without causing mercurial poisoning, and silver or copper coins are equally devoid of effect as poisons. They are active only when they are capable of dissociation into ions of the metal or of an oxide. Thus potassium ferrocyanide does not cause any symptoms of iron poisoning when it is injected into a vein, because the iron passes through the body undissociated, and any effects are due to the ferrocyanide ion and not to the iron. In the same way compounds of the metals with ethyl and methyl, such as lead triethyl, have an action quite different from that of lead, as long as they remain undecomposed in the tissues, but eventually induce metallic poisoning, as they are broken up into bodies from which the lead or lead oxide ion can be dissociated.

The action of the heavy metals consists of two parts, the local effects induced at the point of application, and the general effects which follow the absorption of the poison into the blood and tissues. Either of these may be produced alone by suitable preparations and modes of administration, and they are to be regarded as entirely independent of each other.

The Local Action of the heavy metal series is due to the formation of protein combinations. When the salt of the heavy metal is added to a solution of egg albumin, or similar protein, a precipitate is at once formed of metallic albuminate. The proteins apparently play the rôle of acids, forming insoluble salts with the metals, but these salts are not generally of definite chemical composition, for the percentage of metal contained in the albuminate usually varies within

[illegible]
double salts. Metal + protein = albuminate which protects against action of the acid, which acts as an irritant, or even a corrosive.

wide limits; in some cases, however, definite compounds have been formed.

The albumin displaces the original acid of the salt, which may be entirely removed by prolonged washing. The albuminates of the metals are insoluble in water, but most of them are soluble in excess of protein or of the metallic solution, and many of them may be dissolved in solutions of neutral salts such as chloride of sodium. In the albuminates formed by the addition of salts to protein solutions, the metals are combined in the same way as in inorganic salts, and may be detected by their usual reactions. Thus iron albuminate is rapidly blackened by the presence of ammonium sulphide, because ferrous sulphide is formed from it exactly as from any of the inorganic salts. On subjecting these albuminates to certain chemical manipulations, however, the metal seems to become more firmly attached to the protein, for ammonium sulphide acts on it much more slowly. The metal is then said to be masked, because its presence is not so readily detected as in ordinary combinations. Partially masked preparations have been formed artificially, but in the body the process is carried much further, for in many of their protein compounds the metals cannot be detected by any of the ordinary tests, however long the reagents may remain in contact with them, and their presence is recognized only when the protein is destroyed by heat or other similar agencies.

When a solution of a metallic salt comes in contact with a living tissue, such as the mucous membrane of the mouth or stomach, the albuminate is at once formed, and the acid with which the metal was combined is set free. The more completely dissociated the ions of the salt are, the more rapid is the reaction with protein, and the more intense the local action. Thus the more readily ionized inorganic salts act more strongly than the organic ones which are slowly dissociated, and these in turn are more liable to cause marked local changes than the double salts, which are dissociated with difficulty.[1] Other factors determining the nature of the local action are the character of the precipitate and the activity of the acid formed, the latter again varying with the extent to which it is dissociated into ions; it therefore exercises the same astringent or corrosive effects as if it had been applied uncombined, but its action may be modified by the presence of a layer of metallic albuminate protecting the surface. Thus when a weak solution of lead acetate is applied to a mucous membrane, the metal forms an albuminate with the proteins lying on the surface and in the more superficial parts of the cells. This albuminate forms a continuous sheet over the mucous membrane, and the very dilute acetic acid formed is incapable of inducing any reaction. If a stronger solution be applied, however, the metallic precipitate extends more deeply into the cell, while the acetic acid, being more concentrated, exercises some irritant action. As the concentration increases,

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[1] *Pauli.* Bedeutung der Ionentheorie f. d. physiol. Chemie, 1901.

According to acid comb. with metal, action may be astringent or corrosive. Hg ppt is flaky & sol in excess protein – hence corrosive. Specific toxicity too. Alum if dry abstracts water rapidly. So gt. variation. Chlorides & nitrates easiest dissociated so very corrosive. Sulphates, iodides less so. Acetates, tartrates, citrates least.

the deeper parts of the epithelial cells are coagulated, and at the same time the acid becomes more destructive, so that eventually the superficial layer of the epithelium is killed and the deeper layers are attacked. The acetate of lead may thus act as an astringent, covering a mucous surface with a protective pellicle of insoluble albuminate, as an irritant, which induces an increase in the circulation of the part, a more rapid division of the cells and an effusion of liquid, or as a corrosive, involving the superficial layer of cells, and sometimes even the deeper ones in its destructive effects.

When the nitrate of lead is applied, the astringent effect is much less evident, the irritant and corrosive more marked, because the salt is more readily dissociated and the reaction is therefore more rapid, and in addition the nitric acid is much more corrosive than acetic acid. The same metal attached to different acids may therefore induce very different effects, in the one case acting chiefly as an astringent, in the other as an irritant and corrosive.

The character of the precipitate formed also determines to some extent the local action of the metallic salts. Thus the salts of mercury are more irritant and corrosive than those of the other metals, partly perhaps, because the precipitate is less continuous and more loose and flaky, partly because it is soluble in excess of protein, and therefore allows the unattached molecules to penetrate deeply, while the lead albuminate remains on the surface of the membrane. The metals also differ in their toxicity, and a trace of mercury is sufficient to kill a cell, whereas a larger amount of lead may be absorbed by it without injury.

In addition salts which have a very strong affinity for water withdraw fluid from the cells, and thus act more strongly on them than others which have not this character; for example dried alum is much more destructive to the tissues with which it comes in contact than alum containing its ordinary water of crystallization.

The different metallic salts therefore vary in their local action within wide limits—from the formation of mildly astringent membranes to the production of widespread necrosis and destruction of tissues.

The insoluble salts come into less intimate contact with the tissues, and have much less effect; but many of them are slowly formed into albuminates and may then act as irritants or astringents.

The most powerful corrosive salts of any metal are those which are most rapidly dissociated into ions, that is, the chlorides and nitrates, provided they are soluble. The sulphates are much less irritant, because they are less readily dissociated, and perhaps because the sulphuric acid may fail to penetrate the cells owing to its being less volatile and its anion having less permeating power than that of hydrochloric or nitric acid. (See page 542.) The iodides and bromides are generally regarded as less irritant than the chlorides, but are less frequently used and less well known.

[illegible] ~ comb. effect action — Pb most astringent, then Fe, alum.
Cu-Zn, Ag. Hg little. Must be sol.-fraction -

The least corrosive of the salts of the metals are those formed with the slowly dissociated organic acids, such as the acetates, tartrates or citrates. When these are united with a metal which in itself is not a very active poison, such as lead, they are almost purely astringent. On the other hand, the acetate of silver or of mercury tends to be irritant and corrosive, from the poisonous action of these metals on the tissues. In any case, the acetates are less irritant than the corresponding chlorides and nitrates, provided these are equally soluble.

The local action also varies in the same salt of different metals. Lead is the most astringent of the metals ordinarily used in solution, while mercury salts have little or no astringent action, owing to their specific poisonous action on the cells. Iron and alum approach most nearly to lead, then copper, zinc and silver, and at a longer interval mercury.

It is impossible to arrange the metallic salts as either astringents or irritants, because in every instance the effect varies with the concentration, and with many other features, such as the condition of the surface to which they are applied, and the quantity of protein with which they come in contact before they actually reach the living membrane.

Of the salts in common use, the most astringent are lead acetate and alum; the most irritant are the perchloride and the nitrate of mercury, the chlorides of zinc, copper, tin and antimony, while the chlorides of iron, sulphates of copper, zinc, iron and manganese, the acetates of copper and zinc, and the nitrates of silver and lead are astringents when applied in very dilute solution, but tend to irritate and corrode in large quantities. In most cases the effects of the last group are made up of a mixture of astringent and irritant action.

The insoluble preparations of mercury tend to irritate and corrode the surfaces to which they are applied, but the insoluble salts of the other metals are generally astringent. It is difficult to determine how far the so-called astringent and protective action of these insoluble substances is due to the formation of albuminates, and how far to their acting mechanically as protective coverings over irritated surfaces, but the latter factor is undoubtedly the more important in many instances.

The precipitation induced by the astringents involves only the surface layer of cells, but the membrane formed protects the part from mechanical and chemical irritation, and thus lessens congestion and inflammation. In addition several authors[1] have found that the astringent salts contract the vessels of the frog's mesentery by direct action on their coats, and have inferred that the same constriction is induced in the mucous membranes, when they are applied to them. Schütz[2] found that the secretion of the frog's skin and tongue is lessened when these parts are washed with astringent metallic salts,

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[1] *Rosenstirn*, Rossbach's Pharmakologische Untersuchungen, ii., p. 84. *Heins*, Virchow's Arch., cxvi., p. 220.

[2] Arch. f. exp. Path. u. Pharm., xxvii., p. 202.

Over infl. membranes. may constrict vessels & cut off secretion as well as protect. With exception of Hg. the metals are only slightly absorbed — sym. from local irritation & corrosion. Absorbed best from raw or hyperaemic surface. Excreted very slowly so accumulation liver, kid., spleen, bone marrow → intoxic. Excreted by lower g.i. epithelium: also urine etc.

and it is quite possible that when these are applied to inflamed membranes, they may constrict the vessels and lessen the secretions, as well as form a protective membrane. When irritation is induced, the vessels of course dilate, and congestion and exudation follow.

The local action is due to the formation of albuminate compounds and the liberation of acid. If the metal be applied in the form of an albuminate, this irritation is almost entirely absent except in so far as the poisonous action of the metal may cause necrosis and consequent irritation and inflammation. The double salts of the metals are also less liable to irritate, because they do not precipitate albumin, and their dissociation only occurs slowly and is not confined to the point of application. Of course if these double salts are decomposed by acids, as in the stomach, they may act as irritants.

The salts of the heavy metals are often only slowly **Absorbed.** Mercury is again an exception, but even mercury does not induce general symptoms until many hours after its administration. The other metals given by the mouth pass through the alimentary canal for the most part unabsorbed. In recent years it has been disputed whether iron, manganese, copper and other metals are absorbed at all, but investigation with more accurate methods has shown that iron and manganese pass into the tissues from the alimentary tract, and it seems probable that a small proportion of most of the metals finds its way into the blood. At the same time there is no question that the great proportion of most of the metals passes through unabsorbed, and is devoid of any effect except from its local action. It is probable that the small quantity taken up by the stomach and intestine is first formed into protein compounds in every instance, but there is very little known as to the process. When there is any lesion of the stomach and intestine, and particularly when the salt induces irritation and congestion itself, much more of the metal is taken up than by the normal epithelium. But even in the most favorable circumstances little of the metal is absorbed, and in acute poisoning the symptoms arise from the local irritation and corrosion and only to a smaller extent from the general action of the metal.

If the absorption of the metals is slow, their **Excretion** progresses even more gradually, and repeated administration leads to their accumulation in the tissues and thus to intoxication. The metal seems to leave the blood very rapidly, and to become stored up in various organs, chiefly the liver, to a less extent the spleen, kidney, and bone marrow. While some of the metal is deposited in the liver and other organs, another part is excreted, for the most part along the alimentary tract. Thus it is found in the saliva and gastric secretion, to a much larger amount generally in that of the lower parts of the small intestine, in the cæcum and in the large bowel. A comparatively small amount escapes with the urine. Some metals have been detected in very small quantity in the milk, and there is reason to suppose that traces are eliminated by the other cutaneous secretions.

The **General Action** of the heavy metals in man is often elicited

lay in sym. due to slow absorption of G.I. Chief sym., G.I.; CNS
m. vomit. purge, pain, oedema & hemorrhage of mucosa of G.I. - Little
ttle excreted by kid. yet are diuretics small doses. Large doses infl. Alb.
blood casts finally cirrhosis

only by their prolonged ingestion, but it has been studied in animals by the intravenous or subcutaneous injection of the albuminates or of the double salts, which do not precipitate the proteins. The ordinary salts cannot be used, because the precipitated albumin of the blood causes embolism, and this obscures the symptoms. The symptoms of acute metallic poisoning elicited thus in animals generally resemble fairly closely those of chronic poisoning in man. Of course the anatomical lesions induced in the latter by the constant presence of small quantities of metals in the nutritive fluids, can only be induced to a limited extent in such experiments.

Even when the heavy metals are injected into the blood in considerable quantity, the symptoms are often late in appearing, in the case of aluminium only after several days, so that the slowness of the absorption from the intestine is not the only explanation of the delay in the onset of the intoxication.

The general symptoms of metallic poisoning, as distinguished from those due to the local action at the point of application, arise chiefly from the central nervous system, and from the excretory passages—the alimentary canal and the kidney. Metallic poisoning always induces disturbance of the **Stomach and Intestine**, manifested by loss of appetite, pain and discomfort in the abdomen, nausea, vomiting and purging. In some cases no lesion of the canal is observed post mortem, but in the great majority congestion and swelling of the mucous membranes of the stomach and intestine is seen, or the whole surface may be covered by a diphtheritic membrane composed of necrosed cells and inflammatory exudate. Beneath this, hæmorrhages occur, and if the animal live long enough, ulcers are formed, so that the whole condition can scarcely be distinguished from that of dysentery. Some metals act strongly on the mouth and salivary glands, salivation being one of the earliest features of mercury poisoning. The lining membrane of the mouth becomes congested and inflamed, and numerous shallow ulcers are formed in it.

The heavy metals thus seem to have a specific action along the alimentary tract quite independent of the local action induced when they are swallowed. This is connected with their excretions along it, although it seems inadvisable in the present state of knowledge to say that they irritate the digestive tract because they are excreted in it. One or two metals, notably lead, cause constipation and colic when they are absorbed into the blood, but under certain circumstances they too induce purgation.

Another organ which suffers from the circulation of metals in the blood is the **Kidney**. Comparatively little of the metal is excreted in the urine, but it is found that most of this class act as diuretics in small quantities. Somewhat larger doses irritate the renal epithelium, and albumin appears in the urine, along with casts and, in severe cases, blood cells and hæmoglobin. If this irritation of the secretory cells be long continued, it sets up a secondary inflammation of the interstitial tissue, and cirrhosis of the kidney results.

dil. of intest vessels, + direct action on circulatory system lowers b.p. Diarrhoea & poor chete metabolism = loss of wt. Stim + convulsions or paralysis are cns. sym. Hg + Fe for absorb. Others for irrit caustics & styptics

The **Circulation** is differently affected by different metals. The heart is often affected only in the last stages, and it is impossible to determine how far its failure is due to direct action, and how far to the disorder of the nutrition. The blood-pressure invariably falls towards the fatal issue of the intoxication, and as a general rule, a slow fall is observed from the beginning. This fall in blood-pressure may doubtless be induced by different factors in the different forms of intoxication, but there is no question that it is partly due to the dilatation of the vessels of the intestines and stomach from the inflammation of these organs. In acute general poisoning in animals, many of the metals cause a great fall of blood-pressure, which has been ascribed to their paralyzing the walls of the smaller arterioles and capillaries.

Several metals have been found to lessen the alkalinity of the **Blood** by increasing the amount of lactic acid in it, but this does not seem a common feature in metallic poisoning. The general malnutrition from the gastro-intestinal action renders it impossible to determine whether the metals alter the metabolism of the body through directly affecting the cells, but it is not improbable that this is the case, for the loss of weight is often too rapid to be explained by the starvation alone.

The **Central Nervous System** is always affected more or less by the presence of the metals in the blood. As a general rule, the symptoms are a mixture of those of stimulation of certain divisions with those of paralysis of others. Several metals induce disturbance of the psychical centres, manifested in delirium, hallucinations and mania, or in stupor and coma. Convulsions of all forms indicate that the motor areas of the brain, the basal ganglia and the spinal cord are affected; thus epileptiform convulsions, chorea, clonic and tonic spasms occur from metallic poisoning. In several instances actual lesions of the brain cells have been shown to be caused by the ingestion of the metals. They often cause general weakness, or paresis of certain groups of muscles, and in addition to their specific action on the nervous centres, they may induce a peripheral neuritis (lead). The muscles do not seem to be so readily affected in general poisoning, although a solution of a non-irritating metallic salt paralyzes muscles suspended in it.

Therapeutic Uses.—In therapeutics only mercury and iron are largely employed for their effects after absorption, while the others have a more or less extensive use for their local effects as astringents, irritants, caustics or styptics. Iron is not prescribed for its general action on the organs, but to supply the place of food-irons in the formation of hæmoglobin. Mercury is used for its specific effect in syphilis, and some of its preparations have been advised as diuretics. Not infrequently the local action of the heavy metals is supposed to be induced after absorption, and prescriptions are met with containing lead or iron which are intended to stay hæmorrhage from the

No metal astringent after absorption. Antiseptic when dissociated to metallic ions or when not (spec). Hg + Cu ag. antiseptic. Least bit in water will kill many organisms. Colloids of metals first dissociated.

lungs or from the kidneys. It ought to be recognized, however, that lead or iron is absorbed only in minute quantities, and that they have no predilection for the bleeding points. If they were capable of coagulating the blood after absorption, and thus stopping hæmorrhage, they would certainly do so in the portal circulation and would not be carried to the lungs or kidney before they acted. As a matter of fact, however, they never reach the blood except in forms in which they have no astringent or styptic action.

Many of the metallic salts are powerful disinfectants, partly no doubt from their coagulating the proteins of the microbes, but also from a specific poisonous action on them, which is quite distinct from their precipitating action. As a general rule the antiseptic power varies with the amount of dissociation of the salt, that is, with the number of metallic ions present in the solutions, although the undissociated molecule also seems to have some influence, and a salt which is dissociated with difficulty may in some instances make up for this drawback by the more intense toxicity of the metal.[1] The most widely used metallic antiseptics are the mercurial salts, in particular the perchloride, but other metals have recently begun to play a more important rôle in surgery than heretofore. Almost incredibly small quantities of some of the metals have been found to be rapidly fatal to some of the algæ, the bacteria, and the infusoria. Thus one part of the perchloride of mercury in one million parts of water kills spirogyra, one of the simpler algæ, and water distilled from copper vessels is rapidly destructive to it. Israel and Klingmann[2] hung small pieces of copper foil in water for a few hours, and then diluted this water a hundred times and found it still poisonous to many lower organisms. Silver was less active and lead still less so. The amount of copper in the original solution was too small to be recognized by any chemical test, much more so than in the further diluted portion. These results, which were first obtained by Naegeli, and which have been confirmed by other observers besides Israel and Klingmann, indicate that certain lower organisms are much more sensitive to the action of copper, and probably of other metals, than the more highly organized plants and animals. Further examination of their effects as disinfectants in medicine and surgery is certainly desirable. Other curious effects on the growth of bacteria have been observed by Bolton and Brown,[3] who found that a piece of metal placed on a culture of microbes in gelatin causes curious alternating zones of intense growth and of sterility. These observations have recently been extended by Thiele and Wolff,[4] who state that silver, mercury and copper plates prevent the growth of microbes owing to minute traces of these metals being dissolved in the medium. Several other heavy metals—iron, lead, zinc, tin, gold, platinum and aluminum—proved

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[1] *Krönig u. Paul.* Ztschr. f. Hygiene, xxv., p. 1.

[2] Virchow's Arch., cxlvii., p. 293.

[3] Transactions of the Assoc. of Amer. Physicians, xii., p. 488.

[4] Arch. f. Hygiene, xxxiv., p. 43. *Foa and Aggazotti.* Biochem. Ztschr., xix. *Moore and Hawks.* Biochem. Journ., iii., p. 313.

Antimony – tartar emetic · on skin papules etc · Hypo – gt pain & corro
As emetic – vomit. perspiration, pulse up, salivation. diarrhoea, cyanosis, depress
collapse death

devoid of action. A practical application of this bactericidal action of the metals has been made by the introduction of solutions of colloid forms of silver and mercury as antiseptics. Some of these colloid metals have proved destructive to simple organisms in extremely dilute solution, while in more concentrated forms they are inferior to the ordinary salts of the metals. The so-called colloid solutions generally contain some of the metal in the form of salts, and there is every reason to believe that these colloid forms like the ordinary pure metals have no action until they are changed to dissociable salts, which exert their usual effects in the tissues.

I. ANTIMONY.

The preparations of antimony played a much more important rôle in therapeutics in the earlier part of last century than at the present time. In many respects they resemble arsenic in their effects, and may be looked upon as forming a link between it and the salts of the other heavy metals. The salt most commonly used is *tartar emetic,* or the double tartrate of antimony and potassium [$K(SbO)C_4H_4O_6$]. The effects of this salt were at one time believed to be due in part to the potassium, but have been shown to be those of the antimony alone. As a double salt it is not readily dissociated and is therefore not so corrosive as the chloride, which is a powerful caustic when applied to the skin or the mucous membrane.

When rubbed on the **Skin,** however, tartar emetic causes redness, and a papular eruption, which later passes into vesicles and pustules. If the application be further persisted in, these pustules may become confluent and form small abscesses, and later cause extensive necrosis and ulceration of the skin. The points of origin of the papules are the openings of the cutaneous glands and the hair follicles. When injected hypodermically, tartar emetic causes intense and lasting pain, and very often suppuration and sloughing, which may involve the underlying muscles.

Symptoms.—Tartar emetic has a slight, acrid taste, and in very small quantities causes no symptoms, except some perspiration. In somewhat larger doses its ingestion is followed by nausea and vomiting, with very marked depression and the usual accompaniments of emesis, such as salivation, profuse perspiration and acceleration of the pulse (see Apomorphine, page 240). In antimonial poisoning the vomiting is violent and continuous, the ordinary contents of the stomach being first evacuated, and then a slimy mucous fluid, which may later contain blood. In some cases it is said that no gastric symptoms are observed, but these must be exceedingly rare. The vomiting is accompanied by profuse watery diarrhœa, resembling that of arsenical poisoning, and by great muscular weakness and collapse. The pulse may be somewhat accelerated at first, but is weak, and later becomes slow and irregular. The skin is cold and covered with clammy perspiration, and cyanosis of the face and

Vomit - local irrit. Gi. oedema hyperaemia, peeling of epith. same as in A

extremities is generally marked. The respiration is slow and may be irregular, the voice weak and husky, the temperature is depressed, and the patient falls into a comatose condition, which deepens, until after a few weak convulsive movements the respiration ceases. The urine is sometimes increased in the beginning of the poisoning, but later may become scanty or entirely suppressed. It often contains albumin.

The minimum fatal dose of tartar emetic is doubtful, as the greater part of the poison is generally removed by vomiting. Recovery has been observed after very large quantities, while in other cases 0.1 G. (2 grs.) has proved fatal.

Chronic antimonial poisoning is very rare and difficult to diagnose. The symptoms are depression, headache, giddiness and confusion, drowsiness and indistinct sight. The appetite is bad, and the patient complains of heaviness, discomfort or pain in the region of the stomach, general weakness and exhaustion. Profuse diarrhœa may be present, rapid loss of flesh, albuminuria and finally collapse. Pustular eruptions have been observed from the prolonged internal use of tartar emetic.

Action.—Many of the symptoms of antimonial poisoning, the profuse perspiration, salivation and, to some extent at least, the collapse, are manifestly secondary to the **Emetic Action,** and the cause of the vomiting has, accordingly, been repeatedly investigated. It may be stated at once that some authors attribute the vomiting to a central action, but that the majority are inclined to regard it as mainly due to irritation of the stomach. Large doses of antimony affect the stomach and bowel in the same way as arsenic, inducing hyperæmia and swelling and loosening of the epithelium, but smaller quantities such as are used in therapeutics do not seem to cause any obvious lesion. It is found that tartar emetic injected hypodermically or intravenously causes nausea and vomiting, but much larger quantities are required than are requisite when the drug is given by the mouth. This indicates a direct action on the stomach, rather than on the centre for vomiting, and this view is supported by the fact that antimony is found in the stomach and intestine when it is injected intravenously. The obvious explanation would therefore seem to be that antimony given by the mouth acts as a gastric irritant, and causes vomiting, while when it is injected intravenously it is carried to the stomach, and again causes irritation with the same result. The whole of the antimony swallowed acts at once on the stomach, while only a part of that injected exerts its action on it, and larger doses are therefore necessary when the poison is administered in the latter way.

This explanation is opposed, however, to an observation made by Orfila, who found that when the stomach was excised and replaced by a dead bladder, tartar emetic still caused the movements of vomiting, which even expressed the fluid in the bladder. Of course no antimony could be excreted into the bladder and no irritation or reflexes could arise from it. Again Mosso states that when the vagus nerves are cut below the diaphragm, tartar emetic fails to cause vomiting when it is swallowed, but large doses have their usual effect

As + Sb spec. irritants to bowel.

when injected into a vein. These observations appear at first sight to indicate that tartar emetic acts centrally, but it has been suggested that although the poison could not act on the stomach in Orfila's experiment it might cause vomiting by causing irritation of some other part of the alimentary tract. As regards Mosso's results, the relation of the vagus nerve to vomiting is still so obscure that it is dangerous to draw any inference from such experiments. On the whole the evidence goes to show that the emesis is due to irritation of the gastric mucous membrane by the antimony.

The action of tartar emetic on the **Stomach** has been explained by supposing that the acid gastric juice decomposes the double salt and that the chloride thus formed acts as a corrosive in the same way as the chlorides of the other heavy metals. This, however, fails to explain the fact that the same effects are met with in the intestine, in which no such acid fluid exists, and that vomiting is induced readily when the gastric juice is neutral in reaction (Mosso). A more probable explanation is that antimony has a specific irritant effect on the mucous membranes of the stomach and bowel, similar to that of arsenic. The irritation is greater, however, and is induced more rapidly, so that vomiting is caused much more easily. At the same time, antimony is more slowly absorbed than arsenic, so that its action remains confined to the stomach, and as the vomiting removes much the greater part of the poison, the intestine remains unharmed except when large quantities have been swallowed and the emesis is from any cause insufficient. In chronic poisoning ulceration of the small intestine is said to occur, especially around the solitary follicles and Peyer's patches.

The acceleration of the **Pulse** seen after tartar emetic is due for the most part to the emetic action and not to the absorption of the drug. When injected into a vein in animals, antimony causes a slow and weak pulse, although this is preceded in some cases by slight acceleration. The action is a direct one on the cardiac muscle, as may be seen by perfusing an excised frog's heart with blood containing some tartar emetic. The cardiac nerves do not seem to be affected.

The **Blood-pressure** falls throughout the experiment, partly owing to the weakness of the heart, but chiefly owing to an action on the vascular mechanism similar to that described under arsenic. Here again it is doubtful whether the effect is due to the vasomotor centre or to the peripheral nerves and muscle of the vessels, but the latter are certainly involved, for stimulation of the spinal cord fails to contract the mesenteric vessels.

The **Respiration** is often slightly accelerated at first, and may be shallow and irregular from the nausea; but in cases of poisoning it becomes slow and labored, and eventually ceases along with the heart. The respiratory centre is perhaps affected directly to some extent, but the changes in the breathing are probably due for the most part to the disturbance of the circulation, and to the action on the alimentary canal. The statement made by some of the older writers that antimony caused hepatization of the lungs has been shown to be incorrect.

The **Central Nervous System** is depressed by antimony in the frog, spontaneous movements persisting after the reflexes have disappeared, according to some authors. This has been interpreted to mean that antimony paralyzes the sensory part of the cord or its connection with the motor cell, while leaving the connections between the latter and the brain intact; but the statement

Vomiting increases perspiration, saliva, resp muc. secretion -
a destroys trypanosomes of blood. Metabolic effects same as As

itself requires further confirmation. The paralysis is due to the direct action of antimony on the nerve cells and not to the disordered circulation, for frogs poisoned with antimony are paralyzed sooner than others in which the circulation is entirely destroyed by the excision of the heart. The effect of antimony on the central nervous system of the mammals is more obscure, for it is impossible to ascertain how far the changes are due to direct action and how far they are attributable to the disturbance of the circulation and the alimentary canal. There is reason to believe, however, that the poison depresses to some extent the nerve cells here also. According to Schaffer, the cells of the spinal cord undergo a degeneration marked by the disappearance of the chromatin in chronic antimonial poisoning.

The **Depression** and **Collapse** of antimony poisoning are caused by the gastric effects and the slowed circulation acting on the central nervous system, and not, as is sometimes stated, to the peripheral nerves and muscles being affected. The voluntary muscular tissue is undoubtedly weakened to some extent in the frog, but only after large doses and at a late stage. The muscles then contract somewhat more weakly than normally, and are more readily fatigued.

Many of the **Secretions** are increased by tartar emetic, such as the perspiration, the saliva and the mucous secretion of the respiratory tract. This is not due to any direct action on the glands, for the same effect is induced by anything which causes vomiting. (See Apomorphine, page 240.) The urine is sometimes increased by antimony, at other times it is diminished or suppressed. This is perhaps due to a preliminary stimulation of the renal epithelium, which passes into acute irritation when much of the drug is absorbed. The action on the urinary secretion is not very marked, however.

The irritant action of tartar emetic on the **Skin** when it is applied to it in ointment, has been explained by the double salt being broken up by the acid formed in the decomposing secretions, and an analogy has been drawn between it and the irritant effects in the stomach. This accounts for the formation of pustules at the openings of the skin glands, but the double salts of other metals, which would form irritants in the same way as tartar emetic, have no special effect on the mouths of the gland ducts. Nunn finds a specific effect on the skin of the frog when tartar emetic is injected, similar to that induced by arsenic, but more rapid in its onset, and this may explain the pustulant action. A pustular eruption is said to be induced in some cases when antimony is taken internally. Pustules also occur in the œsophagus when tartar emetic is swallowed, and irritation of the mouth and swelling of the lips have been observed.

Antimony is much less poisonous than arsenic to most of the protozoa, but is found to possess the same extraordinary affinity for certain pathogenic organisms, notably the trypanosomes of the blood, which it destroys in solutions as weak as one in 500,000.

The effects of antimony on the **Nutrition** have not been so carefully examined as those of arsenic, but, as far as is known, present a strong resemblance to them. Thus fatty degeneration of many organs is induced by its prolonged use, the nitrogen of the urine is found to be increased and the glycogen disappears from the liver. Very small quantities of antimony given repeatedly are said to increase the glycogen and fat of the liver, without apparently altering the nitrogen of the urine.

The fall in **Temperature** after antimony is often very considerable, amount-

Is very slowly absorbed from m.m. or skin. $SbCl_3$ violent corrosive
Rarely used as emetic as great depressant. Used to increase secretion
in dry bronchitis

ing in animals to 6° C. in the course of a few hours. It is explained by the slowness of the circulation and by the general depression and collapse and profuse perspiration.

Antimony is **Absorbed** from the skin very slowly, and from the stomach and intestine. It passes into the tissues much more gradually than arsenic, however, and its action on the stomach can, therefore, be elicited without danger of its causing general symptoms. After absorption antimony is found in considerable quantity in the liver, which stores it up for some time. It is excreted into the stomach and intestine, in the urine, and, it is said, in the bile and milk.

The **Chloride of Antimony** ($SbCl_3$) differs from tartar emetic chiefly in being a violent corrosive, which combines to form albuminates and thus acts like the other salts of the heavy metals, and also tends to withdraw fluid from the superficial tissues when it is applied in a concentrated solution. The other compounds of antimony act like the double tartrate, except that most of them are much slower in their effects. Stibine or antimoniuretted hydrogen (SbH_3) differs entirely from arsine (AsH_3) in its action, which is, however, equally poisonous. It has very rarely been examined, except in an impure form, and the symptoms are imperfectly known.

PREPARATIONS.

ANTIMONII ET POTASSII TARTRAS (U. S. P.), ANTIMONIUM TARTARATUM (B. P.), tartar emetic, tartarated antimony ($(KSbOC_4H_4O_6)_2 + H_2O$) forms colorless, transparent crystals, or a white granulated powder, without odor, and having a sweet, afterwards disagreeable, metallic taste, soluble in 17 parts of cold water, insoluble in alcohol. Dose as a diaphoretic, 0.002–0.008 G. ($\frac{1}{30}$–$\frac{1}{8}$ gr.); as an emetic, 0.03–0.1 G. ($\frac{1}{2}$–2 gr.).

VINUM ANTIMONII (U. S. P.), VINUM ANTIMONIALE (B. P.), 4 parts of tartar emetic in one thousand (U. S. P.), in 875 parts (B. P.). 0.6–2 c.c. (10–30 mins.), diaphoretic; 4–15 c.c. (1–4 drs.), emetic.

Tartar emetic is also contained in the compound syrup of squills U. S. P.

Antimonii Oxidum (B. P.), (Sb_2O_3), a heavy, gray, insoluble and tasteless powder. 0.05–0.1 G. (1–2 grs.).

Antimonium Sulphuratum (B. P.), Kermes mineral, consists of antimony sulphide (Sb_2S_3) with a small amount of oxide (Sb_2O_3)—an amorphous, reddish-brown powder, odorless, tasteless, and insoluble in water. 0.06–0.3 G. (1–5 grs.).

Pilula Hydrargyri Subchloridi Composita (B. P.), Plummer's Pills, compound calomel pill, 8 grains contain nearly 2 grains each of calomel and of sulphurated antimony. 4–8 grs.

Therapeutic Uses.—Antimony is used to a much less extent in medicine than was formerly the case. In the seventeenth century it was prescribed so widely and was believed to do so much harm, that the graduates in medicine of Heidelberg were required to take an oath never to use it. At present it is used to a limited extent as an emetic, but is slow in action and induces greater depression and more prolonged nausea than the other drugs which are prescribed for this purpose, such as apomorphine, ipecacuanha, or sulphate of copper. It is therefore seldom used to evacuate the stomach in cases of poisoning or of foreign bodies in the stomach or œsophagus. Its expectorant action is taken advantage of in acute bronchitis in which the secretion of the bronchial mucous membrane is insufficient, but it is of less value when the secretion is abundant. In commencing bronchitis tartar emetic

[illegible]

[illegible] ppt. it - Then stomach tube + purge. Lime or Mg will also precipitate it.

strong tea

is sometimes given until vomiting occurs, and then continued in smaller doses and at longer intervals. It has recently been used in trypanosomiasis, especially in sleeping sickness, in which it has been administered by the month, intravenously and hypodermically. It is at least as efficient as the arsenic preparations, but its use is limited by the intense local action, which precludes its subcutaneous injection. Other protozoal diseases, such as syphilis, have also been treated with it, but it is inferior to mercury here.

It is also used as a diaphoretic to some extent in the same doses as are prescribed as expectorants, but it has been almost entirely supplanted by pilocarpine for this purpose.

In acute fever antimony was formerly largely used as a depressant, more especially when delirium was a marked feature. The object was to produce a mild collapse, but the treatment has been entirely abandoned by most authorities, and probably did more harm than good. Acute lobar pneumonia was almost universally treated by tartar emetic at one time and an attempt has recently been made to revive this treatment but without success.

Antimony has been advised instead of arsenic in the internal treatment of skin disease, but it is impossible to state at present how far it is capable of replacing the more widely used drug.

In all cases in which there is marked depression or weakness, in which the stomach or bowel is disordered, or in which the circulation is feeble, the preparations of antimony are contraindicated.

Tartar emetic was formerly used in ointment (one part to four) as a skin irritant, but its continued application has led in several cases to diffuse subcutaneous abscess, and sometimes to necrosis of bone, so that the tartar emetic ointment has passed into desuetude.

In cases of **Antimonial Poisoning,** emetics are seldom required, but the stomach may be washed out by means of the stomach tube, if vomiting is not present, and a purge may be given to remove the poison in the bowel. Tannic acid is used to precipitate the antimony in the stomach, and the tannate formed must be washed out. A form of tannic acid which is usually available in emergencies is strong tea, which is also useful as a stimulant for the collapse. Lime or magnesia may be used to precipitate the antimony instead of tannic acid.

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II. MERCURY.

Mercury, one of the most powerful inorganic poisons, has been used in medicine for a long time and in a large variety of forms. Some

Many forms – diff in local effects only. Sol active – Calomel less so. Absorbed as Hg alb, sol in excess protein, so readily absorbed. Hg itself corros. Cal and [illegible], gives forming Hg albuminate. Not first changed to $HgCl_2$. The metal itself may be oxidized & absorbed

differences are observed in the action of these, but all of them induce the same general results, the differences existing only in their local effects, and being due to the salts differing in solubility and dissociability. A soluble salt, such as the perchloride, comes into more intimate contact with the tissues, and therefore acts more powerfully locally and is also absorbed more rapidly and in larger amount than calomel, which is entirely insoluble in water. Both the local and the general effects of the perchloride are more marked than those of calomel, therefore, but when sufficient mercury in the form of calomel is absorbed into the tissues, the general effects are the same as if an equal quantity had been taken up as perchloride.

Mercury is absorbed and circulates in the blood in the form of the albuminate, which is rendered soluble by excess of protein. The solubility of the albuminate explains the comparatively rapid absorption of mercury and also its greater corrosive action; the acid formed from the salt on its combining with protein may doubtless play a part in the latter, but this is comparatively insignificant as it is not greater than that of an equally soluble and equally dissociable combination of the acid with another metal. The mercurial ion itself is corrosive, and its destructive action is the more powerful because the precipitate formed with proteins is soluble in the surrounding fluids of the body, and the mercurial action is consequently not limited to the surface of a tissue but extends into the deeper cells. The highly corrosive action of the mercury ion has been ascribed to its great affinity for the amino-compounds which are contained in the protein molecule.

The albuminate is formed rapidly when such soluble salts as the perchloride come in contact with the tissues, and the local corrosion is greater and the absorption more rapid than when an insoluble salt is ingested. A good deal of dispute has arisen as to the absorption of the insoluble salts of mercury, and it is frequently stated that calomel is first changed to the perchloride by the action of the hydrochloric acid of the stomach and by the chlorides of the tissues, and that only then is the albuminate formed. There is, however, no sufficient evidence that the perchloride is formed from the chloride, and such a change is not necessary to explain its absorption, for the proteins of the tissues can act on calomel as such, and, forming the soluble albuminate, allow it to be absorbed. It has been asserted of late that when calomel is injected hypodermically, the leucocytes take it up and carry it off as they do any other foreign insoluble body, and it is quite possible that they may take it up in the same way from the alimentary canal. At the same time the quantity of calomel which comes into intimate contact with the tissues is much smaller than in the case of the soluble perchloride, and a smaller proportion of calomel is absorbed therefore. In the same way other insoluble preparations of mercury are absorbed in the form of albuminates, and even the metal may be oxidized and absorbed when it is applied to the living surfaces or injected into the blood in a state of fine division.

absorbed by lungs (Hg vapor). from ointment - gland ducts & hair roots
HgCl₂ poison - suicide, accidents large cavities for disinfection. Burning in g.i.
vomiting, mm. etc in diarrhoea, collapse, circ. failure etc - exhaustion. Anuria
mind clear. Salivation, ulceration. Shock may kill in 1 hr. acute

Acute 3

Thus the inhalation of mercury vapor by the lungs leads to general poisoning, often of a very malignant type, and mercury rubbed into very fine globules, and applied in ointment to the skin, passes into the gland ducts and along the roots of the hairs, and, after being oxidized, is dissolved and absorbed into the tissues, in which it causes the typical mercurial effects.

Symptoms.—Acute Mercurial Poisoning occurs only from the use of soluble preparations, and in particular from the perchloride of mercury or corrosive sublimate. Many cases have arisen from this poison being swallowed accidentally or with suicidal intent, but of late years an almost equal number has arisen from the perchloride being used as a disinfectant wash for large cavities. When corrosive sublimate is swallowed in poisonous quantity, the patient complains at once of the harsh metallic taste, which is followed by burning pain in the mouth, throat and stomach. Nausea and vomiting set in very soon, and the vomited matter may contain shreds of mucous membrane and blood. Diarrhœa and violent tenesmus, with watery or bloody stools, often containing shreds of membrane, may be among the early symptoms, or may only occur after twenty-four hours. These symptoms from the alimentary canal are accompanied by collapse, with a small, thready, sometimes irregular pulse, shallow, irregular, rapid respiration, cold, clammy skin, pinched features, and sunken eyes. The temperature is often subnormal, but sometimes fever is observed, although this is attributed by many to concurrent disease. The consciousness is usually unaffected, but in some cases somnolence, giddiness, or more rarely anxiety and restlessness have been observed. The urine is much diminished and complete anuria often occurs in a few hours. If the urine is not completely suppressed, it generally contains albumin, renal epithelium, casts, and more rarely sugar. Death may occur within an hour from shock, but more frequently the patient survives several days or even one or two weeks, the symptoms of intestinal corrosion and of renal irritation continuing, until he finally sinks from exhaustion.

When acute poisoning occurs from the absorption of corrosive sublimate from wounds, the symptoms of corrosion of the mouth and stomach are absent at first, but the dysenteric symptoms and the renal inflammation are produced in the same way as when the poison is swallowed. Here again the patient may die within a few hours, but more frequently survives for several days, and in the latter case the symptoms towards the end partake of the character of chronic poisoning. In particular, salivation and stomatitis set in in the course of a few days. These also occur when the poison is swallowed, although they are more liable to be overlooked, from the cauterization produced in the mouth by the local action.

Chronic Poisoning.—A much more frequently observed form of poisoning is that induced by the prolonged medicinal use of mercury. It may arise from any of the preparations, and from any form of ap-

Mercurialism – metallic taste, gums swollen, foetid breath, grey gums. Salivation, ulceration, stomatitis even gangrene & jaw necrosis. Fill caries, & keep clean with 2–4% KClO3. May have vomit & diarrh., loss of wt., weakness, esp when by mouth, also loss of appetite.

plication, although some methods of administration are credited with being less liable to induce it than others. Thus inunction with mercurial ointment and the use of calomel internally are both more liable to cause the severer forms of stomatitis than is corrosive sublimate. ? A single hypodermic injection of an insoluble preparation may induce it in susceptible persons, because the mercury is only slowly absorbed, and passes into the tissues as gradually as if it were given by the mouth regularly for several days. This chronic poisoning or **Mercurialism** is due, not to the local action, but to the effects of the drug after absorption. It is much more liable to occur in certain people than in others, but may follow the abuse of mercury in any case, and the cause of the abnormal susceptibility to mercury is unknown. When mercurialism begins to be manifested, the drug ought to be stopped, or the dose much reduced, until the symptoms disappear. Formerly it was believed that the earlier symptoms of mercurial poisoning had to be induced in the cure of syphilis, but in modern therapeutics every effort is made to avoid them. The first symptoms generally arise from the *mouth and throat,* the patient complaining of a metallic taste, and of a feeling of numbness or soreness of the tongue and gums. The breath has an unpleasant fœtid odor, the tongue is swollen and thickly coated, the gums are soft, swollen and often of a dark bluish-red or gray color and the flow of saliva is augmented. If the medication be continued, as was often done formerly, ulcers appear on the gums and on the sides of the tongue where it comes in contact with the teeth, especially if these are carious, and on the mucous membrane of the cheeks; the salivation increases and irritates the lips and the skin where it is exposed to the secretion. If the administration of mercury be still persisted in, the teeth become loose and fall out, gangrene of the gums, lips and throat, and necrosis of part or even of the whole jaw may follow, and may prove fatal by exhaustion and inanition due to the difficulty in swallowing and to the complete absence of desire for food. The milder forms of stomatitis and salivation are observed in a large proportion of cases of syphilis treated with mercury, according to some authors in 30 per cent. or more. It may be avoided, to some extent, at least, by scrupulous cleanliness of the mouth and teeth, by the filling of carious teeth, and by using a 2–4 per cent. solution of chlorate of potash as a mouth wash.

The *stomach and intestine* also suffer in chronic mercury poisoning. The patient often complains of loss of appetite, and occasionally of a feeling of weight and discomfort in the stomach, nausea and vomiting, general weakness and loss of flesh. Colic and diarrhœa are frequently observed, or diarrhœa and constipation may alternate. These symptoms are naturally more liable to occur from the administration of mercury by the mouth than by other channels, as here the action after absorption is reinforced by the direct local effects. Some *fever* is sometimes noted, but this is secondary to the affection of the mouth, bowel or skin, and is not directly attributable to the mercury.

Persisting skin eruptions. Little urine. Cachexia anemia, weakness restlessness. Mercurial erethism in factories = abnormal irritability, shyness weakness, delirium. Tremor first arms & hands then legs. Shooting pains of nerves, local areas of anaesthesia, no muscular atrophy as in As.

Occasionally *skin eruptions* are seen when mercury is given by the mouth, but much more frequently when it is applied to the skin. In the latter case they are not limited to the point of application, although they often begin from it and spread over a large surface of the body. They are said to occur often without any other symptom of poisoning, except the fever and discomfort which they induce themselves. They vary greatly in form, consisting of small reddish spots, large red erythematous surfaces, urticaria, or eczema, each of these occurring alone or in succession, and being usually followed by desquamation. The eruption generally lasts only 1–3 weeks, but in some cases has not entirely disappeared until three months after its appearance, and in others has returned repeatedly afterwards. It is said to have been induced occasionally by a single dose of calomel.

The *urine* is often somewhat increased, but may be decreased afterwards, and it not infrequently contains albumin, although the proportion of cases in which this occurs is much disputed, and the amount in the urine is generally very small. Glycosuria is much rarer in man, but has been frequently observed in rabbits after prolonged treatment with mercury.

It is still a matter of doubt how far the *sexual organs* are involved in mercury poisoning. According to some authorities disturbances of the menstruation and even complete amenorrhœa have been observed, and abortion is also stated to have been caused by it.

A general condition of *cachexia* may be induced by the presence of these disorders, and is marked by pallor, anæmia, emaciation, weakness and restlessness, with a tendency to fainting and disturbed sleep. The pulse is small, weak and quick, sometimes irregular, and the patient often complains of breathlessness.

Affections of the *central nervous system* are rarely induced now by the abuse of mercury in therapeutics, but are mentioned by some of the earlier writers, and still occur in the case of workers in mercury mines, in mirror, barometer and thermometer factories, and in other manufactories in which mercury is used and its fumes are inhaled by the workmen for prolonged periods. One of these affections is the mercurial *erethism,* a condition of abnormal irritability, timidity or shyness, accompanied by great muscular weakness, and sometimes developing into sleeplessness, delirium and transitory hallucinations. Another well-known form is the mercurial *tremor,* which affects the hands and arms first, later the legs, and sometimes extends over all the muscles of the body. Shooting pains along the nerves or in the joints are sometimes complained of, circumscribed areas of partial anæsthesia, amblyopia, anosmia or deafness have been described, and in some cases localized paralysis of the muscles of the arm or leg has been induced. These last differ from the paralysis of lead or arsenic poisoning in the fact that no wasting of the muscles is observed, and the electrical reaction remains normal.

The symptoms of mercurial poisoning, both acute and chronic, in

Sol preparations (HgCl2) esp germicidal. Spec. for syph. ppt albumins
to antiseptic power overestimated.
Human corrosion of mouth stomach etc. Hypo - pain swelling rarely abscess, nec
Corrosion of skin & mm. After absorbed acts esp on GI & kid.

animals, resemble those in man so closely that it is unnecessary to describe them further.

Action.—Lower Forms of Life.—The action of mercury on proteins extends to all forms of living matter. Whenever the metal comes into intimate contact with albumins, it forms the albuminate and destroys life. This poisonous action is naturally much more evident when soluble preparations are used than when the oxides or calomel are in question. Thus corrosive sublimate in a solution of one part in 50,000 destroys infusoria in some 20 minutes, and even one part in one million kills algæ in the course of a few days. The effects of mercury in syphilis are ascribed to its affecting the specific organism in a similar way and here the metal acts in still greater dilution, though the exact amount of mercury present in an active form in the tissues cannot be estimated. Here, as in the case of other specifics (quinine, arsenic, antimony, etc.), mercury seems to have a stronger affinity for the parasite than for the tissues of the host, and even than for nearly related organisms; for mercury has little effect in malaria or trypanosomiasis, that is, it does not injure the organisms of these diseases in the same degree as it does that of syphilis. The bacteria are somewhat more resistant than these forms, but corrosive sublimate is said to delay the development of some of these in a solution of one part in one million, and the anthrax bacillus fails to grow in blood which contains one part in 8,000. A solution of one part in one thousand is generally regarded as capable of disinfecting fluids completely in the course of a few hours, but there is no question that the germicidal power of corrosive sublimate has been much overestimated. Thus Geppert found that the spores of anthrax could be exposed to the action of a one per cent. solution for many hours and still develop as soon as the mercury was entirely removed. There is no doubt, however, that corrosive sublimate and the other soluble salts of mercury are among the most powerful antiseptics at present available. The insoluble preparations are less poisonous, owing to the difficulty in bringing them into intimate contact with the microbes.

In the **Higher Animals and in Man** the same destructive effects are induced by the mercury preparations. The corrosion of the mouth, throat and stomach when the perchloride is swallowed, has already been mentioned. When it is applied to the other mucous membranes, similar effects are obtained, and when it is injected hypodermically, even in dilute solution, it induces intense pain, swelling and inflammation, which is rarely followed by suppuration, but which may result in the formation of cicatrices. Stronger solutions injected into animals often cause the formation of cheesy abscesses, and even dry necrosis of the skin and underlying tissue. The hypodermic or intramuscular injection of insoluble preparations is more liable to cause abscess formation, because the mercury is slowly absorbed and has therefore more time to induce its irritant effects.

When solutions of corrosive sublimate are applied to the skin, they

Salivation is direct action of Hg on secretory apparatus. Not reflex from mouth. Ulcers, esp. about caries. Some gastric congestion. Hg secreted in saliva may disarrange digestion. Hg secreted in caecum & colon → hyperaemia, ulcers, perforations, rice water, bloody, mucous stools - constant

cause a feeling of numbness very often; but when very strong solutions come in contact with tender parts of the skin, and in particular, when the salt itself is allowed to lie in contact with it for any length of time, deep corrosion, necrosis and sloughing may follow. Even the insoluble preparations are liable to set up irritation when they are rubbed into the skin, especially if there is any pre-existing tendency to cutaneous eruption.

After absorption, mercury acts more especially on the alimentary tract and on the kidneys, although other organs are not exempt from its effects.

The Salivation and Stomatitis, which are so frequently seen under mercurial medication, are obviously not due to the local action of the drug on its way to the stomach, for they occur equally readily when it is applied by hypodermic injection or by inunction. The salivation is apparently due to the direct action of the mercury on the secretory apparatus, for it often appears before any other symptom and is certainly not the reflex effect of the irritation of the mouth. The saliva is sometimes excreted in enormous amounts, many litres of it being poured out in the course of twenty-four hours. It contains mercury, and has therefore a metallic taste, and tends to irritate the lips and skin where it comes in contact with them. In extreme cases it leads to sleeplessness from its accumulating in the back of the throat and awakening the patient with a feeling of suffocation. The stomatitis is likewise due to the excretion of mercury by the saliva and by the other mucous secretions of the mouth and throat. The irritation caused by the metal leads to excoriations, and these to the formation of ulcers, particularly where microbes are present in large numbers, as around carious teeth. The necrosis of the jaws arises from these ulcers penetrating to the bone and setting up periostitis, for mercury in itself has no specific action on the bone such as has been mentioned under phosphorus.

Mercury has less direct effect on the **Stomach**, though congestion and even small hæmorrhages in cases of poisoning indicate that it is not entirely immune; the loss of appetite and malnutrition in chronic poisoning are ascribed to the presence of mercury in the saliva rather than to its affecting the gastric functions directly. In the **Intestine**, on the other hand, mercury is apparently excreted in large amount, and induces very distinct lesions. The parts affected are the cæcum and colon, while the small intestine very often escapes almost entirely. The action of mercury is evidenced by hyperæmia, redness and swelling of the mucous membrane, which later develop into necrotic surfaces and ulcers along the folds; these lend it an appearance almost indistinguishable from that of chronic dysentery and may eventually end in perforation. The symptoms from the intestine are in accordance with the lesions, consisting in constant purging with very fluid, sometimes rice-water stools, intense pain and tenesmus, blood and fragments of mucous membrane in the fæces.

Small doses of mercurials given by the mouth act as **Purges** causing

Calomel + blue pill — grey powder are insol + good purges as insol in stomach. Irritate intest as there into solution. No pain n griping. Mostly → unchanged. Quick action = green bile stool. Hence a much (also chem) antiseptic. Retard diuretic little action on ferments.

soft stools generally without pain or straining. The insoluble preparations are used for this purpose, as they act least on the stomach, and the mercurial purges par excellence are calomel and the metallic preparations—blue pill and gray powder. This effect is apparently due to their acting as intestinal irritants from their specific action on the intestine. They are not dissolved in the stomach, which is therefore not involved in their effects. In the intestine, on the other hand, their longer sojourn and special affinity for the epithelium leads to their partial solution and to their irritant action being developed. A small proportion of these insoluble preparations is absorbed from the intestine, but the great mass is thrown out unchanged in the stools and thus very large doses of calomel sometimes induce no serious symptoms. Mercury acts in the intestine even when the bile is suppressed, and the stools are often of a greenish color, which has been ascribed to a metallic compound formed in the bowel, but which is really due to bile pigment. This is ordinarily decomposed by the microbes in the intestine with the formation of the fæcal pigment, but mercury from its antiseptic properties prevents the growth of the microbes, and the bile therefore appears in the stools undecomposed and possessed of its ordinary color.

The mercurial purges, and in particular calomel, have often been credited with increasing the secretion of the **Bile**, but this has been shown to be incorrect, for Stadelmann (in animals) and Pfaff (in man) found that they had no effect on the secretion escaping from a biliary fistula. The belief probably arose from the green color of the stools, but this, as already mentioned, is due, not to the increase of the bile, but to its being preserved from putrefaction in the intestine. There is, in fact, no sufficient experimental or clinical evidence that the liver is in any way affected directly by mercury. The "biliousness" which is so often relieved by calomel or blue pill, is due, not to the liver, but to disorder of the alimentary tract.

Mercury has no such powerful effect on the **Unorganized** ferments of digestion as it has upon the microbes, for though large amounts of the soluble preparations precipitate the pepsin in artificial digestion experiments, smaller quantities have little effect. Calomel has no action on the digestive ferments, but retards the putrefaction in the intestine, and thus limits the decomposition of the food. Its antiseptic action is aided by the increased peristalsis which follows its use, and which removes the decomposing mass from the canal. In fact, the lessened amount of double sulphates in the urine which follows the use of calomel may be ascribed as much to its purgative, as to its antiseptic power.

Another organ which is powerfully affected by mercury is the **Kidney**. A moderate dose of calomel induces marked diuresis, particularly in cases in which there is a large accumulation of fluid in the body, as in dropsy from heart disease. In other forms of dropsy, such as that arising from hepatic cirrhosis, or from renal disease, it is less reliable, although it not infrequently increases the flow of urine philitis. Necrosis of tubules glomeruli are acutely inflamed. Lime readily deposited in kidney. Possibly a direct action on heart lowering bp - due to weakness, diarrhoea, etc

in these cases also. When purging follows the administration of the mercurial, less diuretic effect is observed.

In normal individuals and in animals the diuretic action is generally much weaker, although some recent work has shown that it can be elicited easily in rabbits (Cohnstein). In view of the fact that mercurial preparations have an irritant action on the kidney, it would seem that the increased secretion of urine induced by calomel and by other mercurials is most probably to be ascribed to a direct action on the epithelium.

In acute mercurial poisoning, when death does not follow in the course of a few hours, anuria is often observed both in man and animals. This anuria is due to the renal changes, which are found to consist in necrosis of the epithelium of the tubules in some parts of the cortex. The whole organ is congested and the glomeruli are in a state of acute inflammation, but the necrosed tubules are the most prominent feature. Very generally in the rabbit, less often in the dog and in man, these are filled with a deposit of phosphate of calcium, occasionally intermixed with some chalk. According to some pathologists, it is deposited first in the tubules and only when these are filled does it force its way into the cells, but a more probable view is that it is thrown out in the necrosed cells, and as these break up, passes into the tubules. It may be remarked in passing that several other poisons, such as bismuth and aloin, occasionally induce this deposit of lime in the kidneys.

These renal symptoms have been observed most frequently in corrosive sublimate poisoning, either by the mouth, or from absorption from a wound. The more slowly absorbed, insoluble preparations apparently do not often accumulate in sufficient quantity in the blood to induce such severe effects. At the same time, albumin or casts are very often observed in the urine from the treatment of syphilitic patients with mercury in any form, although it is stated that this is less liable to occur when soluble preparations are injected hypodermically than after inunction or the use of insoluble salts subcutaneously. The more marked the action on the intestine, the less destruction of the kidney is observed in cases of severe poisoning.

The lime deposited in the kidney has suggested the idea that mercury has a specific action on **Bone**, consisting in the absorption of the calcium, and an attempt has been made to demonstrate this action by estimating the lime salts in bone after mercury, and comparing the amount with that of normal animals of the same size. No action on bone has been established, however, and the explanation of the renal deposit as due to decalcification of the bones has been shown to be incorrect by Klemperer, who found that, instead of being oversaturated with lime which it deposits in the kidney, the blood actually contains a somewhat smaller amount of lime than normally. The lime deposited in the kidney is evidently drawn from that normally circulating in the blood; in necrosed tissue from other causes lime is very often deposited, although not so rapidly as in mercury poisoning. Large doses given repeatedly lead to an increase in the size and number of the vessels of the bone-marrow and the fat cells atrophy rapidly; later gelatinous degeneration follows and the cellular elements of the marrow disappear.

In poisoning, intellect clear to last in acute cases. Muscular weakness thru action on centers. Muscles don't atrophy or lose irritability, even if paralyzed - tremor.

Mercury seems to have comparatively little direct action on the **Circulation** in cases of poisoning, and most of the changes in the pulse are to be ascribed rather to the shock and collapse, or in chronic poisoning to the cachexia and malnutrition, than to any direct effects on the heart and vessels; in some cases of acute poisoning, however, patches of fatty degeneration have been found in the heart. In the frog large doses of soluble salts slow and weaken the heart, and mercury salts injected into the blood vessels of mammals have been found to cause a sudden descent of the blood-pressure and paralysis of the heart. Subcutaneously injected into animals, the soluble salts reduce the blood-pressure more gradually, but at the end a very sudden descent to zero occurs. The action is in part on the heart muscle, in part on the peripheral vessels.

The **Respiration** is also only affected indirectly. In chronic mercury poisoning marked breathlessness is sometimes observed and has been ascribed by Kussmaul to the general muscular weakness.

The action of mercury on the **Nervous System** is very obscure. In acute poisoning the intellect often remains clear to the end, and no symptoms pointing to any direct affection of the central nervous system are observed. In chronic poisoning, however, the higher centres are undoubtedly involved in the effects, as is shown by the erethism and occasional hallucinations. The tremor is also of cerebral origin probably, though this is not yet certain, and the general muscular weakness is not due to the peripheral muscles and nerves being affected, but to the alterations in the centres. The paralysis sometimes observed in the arms or legs in workers in mercury, and the areas of partial anæsthesia and the pains in joints probably arise from peripheral neuritis. In some cases, especially where the tremor is marked, the reflex excitability of the spinal cord has been found to be exaggerated, but it is generally unaffected. The muscles do not seem to be acted on directly in either acute or chronic poisoning in man, and even when paralysis is developed, they maintain their irritability and do not atrophy.

A good deal of interest has been manifested in the question whether mercury affects the **Nutrition** in any way except through its action on the alimentary canal. Several authors have stated that the urea is increased by the use of small doses, but the subject is a very difficult one to investigate, for when any save the smallest doses are given, the kidney and bowel are involved in the effects, and the prolonged use of mercury is restricted to experiments on animals and on syphilitics. There seems, however, good reason to believe that very small doses of mercury given for some time increase the nutrition and weight of animals. The cachexia of chronic poisoning may be due in part to a specific action on the metabolism, but it is impossible to determine this point, because the alterations in the alimentary tract are in themselves sufficient to cause such symptoms. Meyer found that mercury lessened to some extent the alkalinity of the blood, probably by the formation of lactic acid in excess.

Changes in the **Blood Corpuscles** have been observed under mercurial treatment in a number of instances, but there is as yet no general agreement as to wherein these consist, and it seems not unlikely that

Long use, Hg in all tissues, esp kidney, intest & liver. Eliminated chiefly thru intest & kid. Gets to foetus. Also in perspir'n milk, saliva, gastric juice & bile.

less usually of ?

the blood reaction in health is different from that in syphilis and that it may vary in the successive stages of the disease. In health the red corpuscles and the hæmoglobin are said to be augmented at first but afterwards diminished, while in syphilis a sharp fall in the amount of hæmoglobin is succeeded by an increase to beyond that present before the treatment. Kuperwasser states that in healthy persons mercury increases the number of newly formed leucocytes but that this is more than counterbalanced by the fall in the older cells; in syphilis he found fewer recently formed leucocytes and more mature ones after mercury.

Mercury has no effect on the **Temperature** in itself, but when stomatitis or skin eruptions are developed, some fever generally accompanies them, while in collapse the temperature may fall several degrees below the normal.

Distribution.—After its prolonged use mercury is found in almost every organ of the body, but larger quantities are found in the kidney, intestinal wall and liver than elsewhere. In cases of acute poisoning through absorption from the subcutaneous tissue or from wounded surfaces, the distribution is the same. The statement that mercury is stored up in large quantities in the bones has not been confirmed by the more recent investigators, but traces are found here, as in the muscles, brain, lungs, intestine and spleen.

Mercury is **Eliminated** by almost all the excretory organs, but most largely by the intestine and kidney. It has been found in small quantities in the perspiration, milk, saliva, sweat, gastric juice and bile, and has been shown to pass to the fœtus in utero through the placental circulation. The excretion in the urine begins within an hour when mercury is injected intravenously, but more slowly by the ordinary methods of administration; for example, after inunction, none may be found for 24 hours. The quantity eliminated daily rises slowly during the treatment and then falls gradually. The excretion is very slow and varies according to the method of administration; there is no question however, that after the usual methods of administration in syphilis mercury is found in the urine for months and in some cases for years after the last dose. No accurate estimation of the mercury excreted in the fæces has been made, but it is believed that less is excreted here than in the urine at first, but that later the greater part may pass out by the intestine. The administration of potassium iodide does not accelerate the elimination of mercury. In the urine the mercury probably exists for the most part in the form of a salt, although some of it may be in organic combination.

Mercury forms very poisonous compounds with methyl and ethyl, which are apparently very slowly decomposed in the organism to ordinary forms, and which have given rise to fatal poisoning in two cases, the symptoms making their appearance only long after the ingestion.[1]

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[1] *Hepp,* Arch. f. exp. Path. u. Pharm., xxiii., p. 91.

Hg in primary & secondary syphilis.
Only allow earliest sym. of poisoning in therapeutics

Therapeutic Uses.—The chief purpose for which mercury is used internally is the treatment of **Syphilis.** Its curative effects in this disease are due to its specific destructive action on the spirochæte pallidum, the organism of syphilis. Long a subject of discussion, its usefulness in this infection is now acknowledged by all who have studied the subject. It is true that mild cases sometimes recover without the use of mercury, but even these run a shorter course if mercury is administered. And in many others, in which the symptoms show no signs of abating under hygienic measures, mercury causes a rapid and permanent improvement. A certain number of relapses undoubtedly occur after the mercurial treatment has been left off, but it seems probable that many of these would not have had even temporary relief without mercury. In a certain proportion of malignant forms mercury is unable to arrest the progress of the disease. And the late syphilitic changes in the central nervous system which are manifested in tabes and in the general paralysis of the insane, are not prevented by the mercurial treatment adopted in the early acute stages.

The effects of mercury in syphilis present many analogies to that of arsenic and antimony in trypanosomiasis; in each a protozoal parasite in the tissues is in some cases destroyed by the specific remedy, and this is fortunately often complete in syphilis; but in other cases a relapse occurs from some of the organisms surviving the first treatment. In the case of the trypanosomes these survivors are more resistant to the specific than the original infection, but this has not been shown to be the case, at any rate in the same degree, in syphilis. A change in the treatment, however, to the iodides, or a combination of iodide and mercury is often advantageous exactly as in trypanosomiasis a new trypanocide may destroy the forms which are resistant to arsenic. Finally it seems probable that protozoa which have reached the central nervous system are not susceptible to the specifics at present in use.

At the present time mercury is administered in small quantities, and syphilologists are agreed that it ought not to be allowed to induce any but the earliest symptoms of chronic poisoning.

A question that is still debated, and which, like the other matters of doubt concerning the mercurial treatment of syphilis, has given rise to an overwhelming literature, is whether mercury ought to be exhibited as soon as the diagnosis of primary syphilis is made, or whether the advent of the secondary stage is to be awaited. Practice differs in this respect, but probably the majority of physicians do not prescribe mercury until some secondary symptom makes its appearance, and then continue its administration until the disease disappears, or until salivation or stomatitis warns against its further use. Some authorities recommend that mercury be continued for months after the secondary symptoms have been relieved, in order to prevent relapse, but this is less rigidly carried out now than in the earlier decades of last century. In tertiary syphilis mercury is generally tertiary, iodides, mercury: in brain & eye. Specific for spirochete Kill it but not tissues. Also $HgCl_2$. May disturb digestion. Inunction rules out stomach, but not secretion by intest.

Inhalation, in mouth, intramuscular, [illegible] - bag in clothing

$Hg + I = HgI$ corrosion!.

considered inferior to the iodides, but when the disease attacks any important organ, such as the brain or eye, mercury is more reliable, or both mercury and iodide may be prescribed together. In hereditary syphilis mercury is much more efficient than iodides.

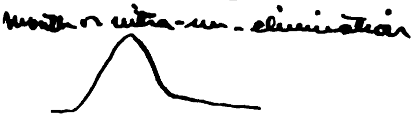
Mercury has been used in syphilis in a large number of forms, and of late years many new preparations and new methods of administration have been proposed. Mercury cures syphilis by destroying the organism, and this object is to be attained by introducing enough of the metal to act on the spirochæte without inducing symptoms from its action on the tissues. The estimation of the metal absorbed by the different forms of treatment is thus of much interest, and a fairly accurate idea of the amount absorbed appears to be given by that excreted. The best clinical results appear to follow from a rapid absorption and prolonged excretion, as, if the stay of the mercury in the tissues is short, relapses are liable to occur. Formerly mercury was given *by the mouth* or by inunction, and apart from the special clinics and the syphilologists, the internal treatment is still the most popular one. The preparations generally used for internal administration are corrosive sublimate, calomel, or the metallic preparations —blue pill and gray powder—the last being used most widely in England. Calomel and the metallic preparations are, however, very liable to induce diarrhœa, from their being insoluble and thus passing into the intestine before being absorbed, and opium is therefore often prescribed along with them. Calomel is also credited with causing salivation and stomatitis more readily than the other preparations, perhaps because it is more difficult to gauge how much of it is absorbed than in the case of the soluble perchloride. Large amounts of mercury have been shown to be absorbed, when calomel and other salts are taken, but the concentration in the blood appears to vary more irregularly from day to day than when other methods are employed. And mercury administered by the mouth is in all cases more liable to derange the digestion than when administered by other channels. Accordingly, *inunction* was introduced to avoid the disturbance of the stomach and intestine caused by the local action of the mercury, while that due to its excretion along the alimentary tract remained unchanged. Mercury ointment is rubbed into the skin and is absorbed in part from the ducts of the glands but mainly by the lungs as vapour. The absorption is slower than by internal administration, but is more regular and lasts longer and there is less disturbance of digestion. The objection to the method is that it is inconvenient and uncleanly, and that it is even less possible to estimate the amount of mercury actually absorbed than when it is given by the mouth. One case of fatal poisoning has been recorded from the ointment being applied to sore hands. Instead of mercury ointment being rubbed into the skin, one of the plasters, or lint containing mercurial ointment (Weylander) may be applied to it, permitting of the continuous absorption of small quantities by the skin and by

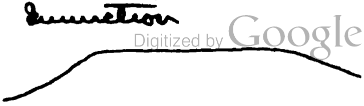
Mouth — derangement of digestion
Inunction — slow absorption — eliminates local mouth & stomach effects. but does attack intestine. Inaccuracy of dosage. Unclean.
Intramuscular — perchloride — insol salts — slow absorb (good) but much pain. possibly ulcer or gangrene.

inhalation of the vapor. Or a mild effect may be induced by mercury in a state of fine division being carried in a bag in the clothing. !

In 1867, Lewin introduced the *hypodermic or intramuscular injection* of a dilute solution of corrosive sublimate, and this has been very widely practised of late years, and with great success. The advantages of the method are the avoidance of digestive disturbance, which is shared by the inunction method, its cleanliness, the more accurate estimation of the amount of mercury actually administered, and the greater rapidity of action. The absorption is very rapid, mercury appearing in the urine in the course of an hour, but the maximum is soon reached and much of the metal is eliminated in two or three days. Its chief disadvantage is the pain caused by the injection, which has to be repeated daily; some inflammation and swelling follow immediately, but no suppuration, when ordinary care is taken; but the pain is very intense and persistent and many patients refuse to continue the treatment. Salivation is said to follow this method more seldom than any other, and relief from the secondary syphilitic symptoms is gained sooner. Lewin continues to use the perchloride solution and prefers it to any of the modifications; sodium chloride or urea are often added to prevent the precipitation of proteins and the consequent local irritation. Others have advocated the peptonate or albuminate, or salts of mercury with an aminoacid, such as glycin, formamide or succinimide. These methods are said to lessen the pain of hypodermic injection, but do not remove it entirely, probably because the various compounds undergo some dissociation in the tissues, and the free mercury ion causes the same irritation as if the perchloride had been injected.

Instead of the soluble preparations of mercury, which necessitate the painful injections being repeated daily, *insoluble salts* have been injected into the muscles with the idea that these being slowly dissolved and absorbed from the seat of injection, a quantity sufficient for several days may thus be given at one time. The immediate pain is less than from perchloride injections, but, as solution takes place, and the mercury attacks the tissues, the part becomes extremely painful, swollen, and inflamed. Suppuration and even gangrene have been developed in a very considerable number of cases, and in others severe or fatal mercury poisoning has been observed. The advantages of the method are that the physician has not to visit the patient every day, and that the injection need only be made once, or at most twice a week. On the other hand, the local lesions are often very severe, and the amount of mercury absorbed cannot be controlled in any way. It has the advantage over the administration per os that the digestion is not so liable to be disturbed. In spite of its drawbacks, this method has gained a wide popularity and is considered more certain than any of the others except the injection of perchloride, which shares its disadvantages. The amount of mercury in the circulation (as measured by that excreted) is subject to less variation than is the case with other methods except inunction, which is much slower in effect. The





Hypo: Calomel in salt sol. or liquid paraffine. finely divided metallic Hg in liquid paraffine; the salicylate & thymol acetate. HgCl₂ +
Purge – calomel, blue pill, grey powder. with or without vegetable purge.

Intravenous In cardiac dropsy. Not in exudates. Calomel, a powders in water

preparations most commonly used are calomel suspended in salt solution or in liquid paraffin, metallic mercury in very fine division suspended in liquid paraffin, the salicylate and the thymol-acetate. The oxides have also been proposed, and many other preparations have received a trial by this method.

Other methods of introducing mercury into the tissues are more rarely employed. The *intravenous injection* of the perchloride has been suggested for the treatment of cases in which there is urgent haste, but is scarcely to be recommended in ordinary infections, as there is danger of embolism; and while the blood contains a large quantity for a short time, the concentration falls very rapidly from the metal being eliminated.

Suppositories of mercury have been used to some extent and are said to disturb the digestion less than the administration per os.

Mercury *fumigations* have also been practised to a limited extent, the vapor of mercury being freed by heating calomel or the sulphide. The patient sits in a wooden tent up to his neck, and the mercury deposited on the skin is absorbed. The method is very cumbrous and the quantity of mercury taken up cannot be controlled.

Mercury was recommended by Hamilton in the beginning of last century in the treatment of **Acute Febrile Affections**, and the greatest abuse unquestionably prevailed in the earlier decades. Later its sphere of usefulness was restricted to the treatment of inflammation of the serous membranes—pleurisy, meningitis, pericarditis, peritonitis—and many physicians still maintain that it checks the effusion and promotes the healing of these diseases. Others deny that mercury possesses any virtues in these cases, and its use is undoubtedly becoming more limited; in acute iritis it is still used almost universally. In these cases it is always administered by the mouth in the form of calomel, blue pill or gray powder.

As a **Purgative** mercury is very frequently prescribed in "biliousness" and in putrefactive diarrhœa. It acts partly from its antiseptic power, but mainly by removing the putrefying contents from the intestine; calomel, blue pill, or gray powder is usually employed with or without the addition of a vegetable purge.

Calomel has proved of only doubtful value as an intestinal antiseptic in typhoid fever, dysentery and other similar conditions.

Calomel and other mercurials have long been known to be of value in cases of **Dropsy.** The best preparation is calomel, given in 0.2 G. (3 grs.) doses three times a day or in 0.1 G. (2 grs.) doses 5–10 times a day. It is of great value in certain cases of cardiac dropsy, but is less reliable in the accumulations of fluid met with in hepatic or renal disease, although here too its administration is sometimes followed by the rapid excretion of the fluid. It does not seem to be contraindicated in chronic nephritis, although its action has to be carefully controlled. It has no effect in removing the exudations of acute inflammation such as pleurisy.

Mercury is used **Externally** as a **Disinfectant** wash in surgical operations, chiefly in the form of the perchloride, but also as the cyanide and oxycyanide. It is irritant to wounds, however, and is liable to be

Irritant to wounds tho $HgCl_2$ used in surgery
Unless syphilitic, contraindicated in profound anaemia, cachexia &
Hg ointments or ~~for~~ dusting powders form HgI_2 if iodides being given
int = acute corrosion (eye)

Lavage, TA. eggs. milk

absorbed when applied to large surfaces, and several cases of fatal poisoning have been recorded from the use of even the most dilute solutions of corrosive sublimate to wash out the uterus and vagina. These preparations, more especially the perchloride, have also the disadvantage of attacking steel instruments.

Numerous ointments have been applied externally in the treatment of **Skin Diseases**, particularly those of a parasitic nature, such as itch, and in condylomata, ulcers and skin diseases of syphilitic origin. These preparations combine a disinfectant with a more or less irritant action, and unlike carbolic acid and its allies, are equally powerful antiseptics in ointments and in water. The least irritant of the pharmacopœial ointments is the mercury ointment; then the oleate, yellow oxide, red oxide and ammoniated mercury follow in order, while citrine ointment is much more irritant and corrosive. Other external applications are the plasters and the black and yellow wash. Ointments containing calomel, corrosive sublimate and other preparations are sometimes prescribed, or calomel may be used as a dusting powder in syphilitic ulcers. The mercury ointments are frequently applied to the eye, the milder ones as antiseptics and slight irritants, citrine ointment to destroy granulations.

Mercurial ointments are sometimes employed to promote the absorption of subcutaneous effusions and to reduce swellings. They are not superior to other irritants for this purpose, however, and have the disadavantage of permitting the absorption of a dangerous poison.

The nitrate of mercury and its ointment (citrine) are sometimes used as caustics for application to the os uteri, condylomata and elsewhere.

Mercury treatment is **Contraindicated**, or requires special caution in cases of profound cachexia, weakness or anæmia, unless these arise from syphilis. Where the digestion is weak, it ought to be avoided if possible, and in cases of tuberculosis there is always the danger that the disturbance of the digestion may accelerate the course of the disease. In severe nephritis it is also to be used with caution, although it is beneficial in some cases, and although some authorities deny that it is injurious even when it has no diuretic action. In pregnancy mercury is not absolutely contraindicated, at any rate up to the sixth month. Later it is liable to injure the patient by its action on the digestion, and in some cases has induced abortion; the child may also suffer from mercurial poisoning. Mercurial ointments or dusting powders have to be used with care when iodides are being administered internally, as the iodide excreted forms the iodide of mercury, and this may cause violent corrosion. Thus in the eye, severe effects have been induced by the application of calomel to the cornea while iodide was being given.

In cases of **Acute Corrosive Poisoning**, the indications are the evacuation of the stomach, preferably by the stomach tube. Tannic acid, or eggs, milk and other albuminous substances may be given to pre-

Hg Poisoning – pot. chlorate used as mouth wash
$HgCl_2$ used in syph in 1%. Hypo 2cc of 0.6%
1:2000 or 1:4000 for hands + wounds. Not for delicate tissues – serous.
corrodes instruments.

cipitate the metal and protect the mucous membrane. The treatment of the later symptoms is the same as that of the chronic form.

In **Chronic Poisoning** the salivation and stomatitis are treated by the use of potassium chlorate solution as a mouth wash, and its free application during mercurial treatment, along with careful brushing of the teeth, is believed by most physicians to hinder the onset of the symptoms. Tannic acid solution is also recommended as a mouth wash. The diarrhœa may be treated with opium, the other symptoms on general principles. In any case the drug ought to be abandoned, or the dose much reduced as soon as the salivation becomes marked. Iodide of potassium and hot baths or sulphur baths are often advised in chronic poisoning with the view of accelerating the elimination of the metal, but careful estimations have shown that they have no such effect.

PREPARATIONS.

2–4 mg.
1/32 gr
1:16 cold water

HYDRARGYRI CHLORIDUM CORROSIVUM (U. S. P.), HYDRARGYRI PERCHLORIDUM (B. P.), CORROSIVE SUBLIMATE ($HgCl_2$) forms heavy, colorless crystals, without odor, but possessing an acrid, metallic taste, soluble in 16 parts of cold water, in 2 parts of boiling water, in 3 parts of alcohol, and in 4 parts of ether. 2–4 mgs. ($\frac{1}{32}$–$\frac{1}{16}$ gr.).

LIQUOR HYDRARGYRI PERCHLORIDI (B. P.) contains $\frac{1}{16}$ gr. in a fluid dr., $\frac{1}{2}$–1 fl. dr.

Corrosive sublimate is one of the most irritant preparations and is rapidly absorbed. It is used internally in syphilis in one per cent. solution and is also injected hypodermically in 0.6 per cent. solution, 2 c.c. (30 mins.) daily. This solution is often made up with 6 per cent. of sodium chloride or urea. Perchloride of mercury is less liable to induce salivation, but disturbs the digestion more than other preparations when given internally, while its hypodermic injection is exceedingly painful. It has induced fatal poisoning in the dose of 0.18 G. (3 grs.), taken by the mouth, but in other cases much larger quantities have been recovered from. It is stated that opium eaters can take enormous quantities without evil effects.

cross tolerance

It is used extensively in surgery as an antiseptic solution (1 in 2,000–4,000), to disinfect the hands, wounds, etc., but is irritant to delicate tissues, such as the peritoneum, and corrodes steel instruments. It is also used in the form of a soap and to impregnate bandages, cotton-wool, gauze, catgut and silk. It preserves its antiseptic action in oils and ointments. It has been used to a limited extent in skin diseases in solution, in baths, or in ointment, as a local application in diphtheria and as an intestinal antiseptic in putrefactive diarrhœa, typhoid fever and cholera.

HYDRARGYRI IODIDUM RUBRUM (U. S. P., B. P.), red iodide of mercury, biniodide of mercury (HgI_2), a scarlet-red, amorphous powder, tasteless and odorless, almost insoluble in water, but soluble in solution of iodide of potassium. 2–4 mgs. ($\frac{1}{32}$–$\frac{1}{16}$ gr.).

This preparation is very seldom prescribed as such, but is frequently formed by prescribing a mixture of corrosive sublimate and potassic iodide, when the iodide of mercury is formed and is kept in solution by the excess of the iodide of potassium. This prescription is often indicated in the transitional period between secondary and tertiary syphilis, and even when the tertiary symptoms are fully developed.

✓ *Liquor Arseni et Hydrargyri Iodidi* (U. S. P., B. P.), Donovan's solution, contains one per cent. each of arsenic iodide and red mercuric iodide. Used as a tonic in syphilitic and other cases. 0.05–0.5 c.c. (1–8 mins.).

Unguentum Hydrargyri Iodidi Rubri (B. P.), 4 per cent.

Calomel - hydrargyri chloridum mite insol H_2O. Salivation.
Little irritation + colic as a purge.
Calomel not to $HgCl_2$ in stomach.

HYDRARGYRI CHLORIDUM MITE (U. S. P.), HYDRARGYRI SUBCHLORIDUM (B. P.), mild mercurous chloride, CALOMEL (Hg_2Cl_2), a heavy white powder, without odor or taste, insoluble in water, alcohol and ether. 0.03–0.3 G. (½–5 grs.) in powder, less suitably in pill form. .03 – .3 g ½ - 5 gr

Unguentum Hydrargyri Subchloridi (B. P.), 10 per cent.

Calomel is contained in the compound cathartic pill U. S. P. (p. 107).

Calomel is used in syphilis (dose, 0.05 G. (1 gr.) thrice daily), but is credited with being more liable to induce salivation than other preparations, and its purgative action often has to be counteracted by opium. A suspension of 1 part calomel in 20 parts of 10 per cent. salt solution or liquid paraffin is often injected into the buttock in syphilis; the dose of calomel by this method is 0.05–0.1 G. (1–1½ grs.) once a week. As a purge and intestinal disinfectant it is of value in biliousness and in the diarrhœa of putrefaction, less so in diseases in which the intestinal wall is the site of infection, as in typhoid fever and cholera. Calomel causes less irritation and colic than most other purges, and small doses are followed by only one evacuation. It may therefore be given where preëxisting irritation of the intestine contraindicates the use of most other purgatives. Calomel is often advised in hepatic affections, but it is a question whether it has any effect here except as a purge. It is of great value in some forms of dropsy, especially those of cardiac origin, in which it is administered in 0.2 G. (3 gr.) doses thrice a day for 2–4 days, and is stopped as soon as the diuresis sets in. The treatment may be repeated if the dropsy returns. Alkalies are often added to calomel prescriptions on the ground that in this way there is less danger of the calomel being changed to corrosive sublimate in the stomach; for the same reason acids are often avoided for some time after calomel is taken. As a matter of fact these fears are quite groundless, as calomel is not changed to the perchloride in the stomach and it is therefore quite unnecessary to add alkalies to calomel.

Calomel has been used externally as a dusting powder for syphilitic condylomata, as a slight irritant to the cornea and as an ointment in pruritus and other skin diseases.

Hydrargyri Iodidum Flavum (U. S. P.), yellow or green iodide of mercury (Hg_2I_2), a bright yellow amorphous powder, tasteless and odorless, insoluble in water, alcohol or ether. 10 mgs. (⅙ gr.).

It has been used in syphilis, with the idea of uniting the virtues of the iodides and of mercury. But the quantity of iodide is altogether inadequate.

HYDRARGYRUM CUM CRETA (U. S. P., B. P.), mercury with chalk, GRAY POWDER, is formed by rubbing up metallic mercury with chalk and honey (U. S. P.) until the mercury is divided into very fine globules, each encased in chalk. It forms a light-gray, somewhat damp powder, without odor and with a sweetish taste from the honey. The mercury (38 per cent. U. S. P., 33 per cent. B. P.) remains in the metallic state, very little oxide being formed. It is insoluble in water, alcohol and ether, and is always prescribed in powder form. 0.1–0.5 G. (2–8 grs.). .1 – .5 g.

MASSA HYDRARGYRI (U. S. P.), mass of mercury, BLUE MASS, BLUE PILL, is formed from metallic mercury by rubbing it with Mel Rosæ, glycerin, althæa and liquorice until the globules are invisible under a lens magnifying ten diameters. The blue mass contains about 33 per cent. of mercury almost entirely in the metallic form. It is of the consistency of pills and is always prescribed in this form. 0.25 G. (4 grs.). .25 g

PILULA HYDRARGYRI, BLUE PILL, the corresponding B. P. preparation, is made up with confection of roses and liquorice by rubbing them with metallic mercury until the globules are no longer visible. 4–8 grs.

These preparations are very largely used as mild mercurial purgatives, the blue pill being frequently reinforced by the addition of one of the vegetable purges. The gray powder is especially adapted for children, and is of value in summer diarrhœa and other similar conditions. Blue pill is often given in cardiac dropsy along with squills or digitalis, but has proved inferior to calomel as a diuretic. Gray powder is held by some authorities to be the best form for the internal treatment of syphilis, and is given in doses of 0.05 G. (1 gr.) 3 to 5 times a day; if necessary, opium may be given to prevent purging. The blue pill may also be used in syphilis and is less liable to purge.

UNGUENTUM HYDRARGYRI (U. S. P., B. P.), mercurial ointment, BLUE OINTMENT, is formed by triturating metallic mercury with lard and suet and oleate of mercury until the globules are invisible when magnified ten diameters. The ointment contains about one half its weight of metallic mercury along with a small proportion of oleate. 50%.

Unguentum Hydrargyri Compositum (B. P.) contains camphor and is somewhat weaker than blue ointment.

Unguentum Hydrargyri Dilutum (U. S. P.) contains 2 parts of mercurial ointment with 1 part of petrolate. 33%.

The famous blue ointment is used largely in many forms of skin diseases, especially in those of syphilitic origin, and was formerly the ordinary treatment for scabies, in which, however, it has been supplanted by balsam of Peru and other remedies, though it is still used occasionally to destroy pediculi. The most important purpose for which blue ointment is applied at the present time is the treatment of syphilis by inunction. For this purpose 2–4 G. (½–1 dr.) is rubbed in daily in different parts of the body, in order to avoid the irritation induced by applying it repeatedly to one spot. A warm bath is taken first, and the patient then rubs in the ointment on the inside of the thighs, next day on the inside of the arms, on the following days on the forearms, legs, abdomen and back, returning to the thighs on the seventh day and repeating the series. The treatment is continued for a fortnight or three weeks. This method has the advantage that the digestion is less affected than when the drug is given internally, but on the other hand, the mercury is more slowly absorbed than by other methods; and no estimate of the quantity really taken up can be formed, as, although the patient is directed to rub it in until the whole disappears, the instructions may be imperfectly carried out. Salivation is not so readily produced as by the administration per os, but when it occurs, it lasts longer and may become severe. One case of fatal poisoning has been recorded from the application of the ointment, but in this case the skin appears to have been broken. Skin rashes are more frequent from inunction than from any other method of application, and finally, the method is extremely inconvenient and dirty. In children the ointment is often applied by spreading it on a bandage, which is then applied around the waist. In skin disease and in very hirsute individuals, the inunction treatment is impossible.

Oleum Cinereum, or gray oil (not official), is a suspension of metallic mercury in liquid paraffin or in lanolin and oil, and is used in syphilis by intramuscular injection. It often is made up to contain 20 per cent. of mercury, and the dose is then 2–3 c.c. once a week. 20%

Oleatum Hydrargyri (U. S. P.), *Hydrargyri Oleas* (B. P.), oleate of mercury, has been used for the same purposes as mercury ointment, but is somewhat more irritant and possesses no compensating virtues.

Unguentum Hydrargyri Oleatis (B. P.), 1 part in 4.

Emplastrum Hydrargyri (U. S. P., B. P.), mercury plaster, is formed in the same way as the ointment by the trituration of metallic mercury.

The plaster is sometimes applied to chancres and to syphilitic ulcers, and has been used instead of the ointment as a treatment of syphilis.

HYDRARGYRI OXIDUM FLAVUM (U. S. P., B. P.), yellow mercuric oxide.

HYDRARGYRI OXIDUM RUBRUM (U. S. P., B. P.), red mercuric oxide.

UNGUENTUM HYDRARGYRI OXIDI FLAVI (U. S. P. 10 per cent., B. P. 2 per cent.).

UNGUENTUM HYDRARGYRI OXIDI RUBRI (U. S. P., B. P.), 10 per cent.

The two oxides are identical in constitution (HgO), but the yellow is obtained by precipitation from the perchloride, the red by oxidation of the metal by means of nitric acid. The red is crystalline, the yellow amorphous, and both are practically insoluble in water and alcohol, but are soluble in acids. The red oxide is more irritant than the yellow on account of its crystalline form, and perhaps also because it often contains some nitrate. The yellow oxide is used in ointment in various diseases of the eye, and both are employed as applications to syphilitic sores, condylomata and chancres, although the red is often preferred for this purpose.

Two famous preparations of mercury are the black and the yellow wash, the former prepared from calomel, the latter from corrosive sublimate by the action of lime water. The black wash, *Lotio Hydrargyri Nigra* (B. P.), contains mercurous oxide (Hg_2O), the yellow, *Lotio Hydrargyri Flava* (B. P.), mercuric oxide (HgO). The oxides are in both cases insoluble and the lotions have to be shaken before application. They are used in syphilitic lesions as local remedies.

Hydrargyrum Ammoniatum (U. S. P., B. P.), mercuric ammonium chloride, white precipitate (NH_2HgCl), is formed by precipitating corrosive sublimate with ammonia, and is a white, amorphous powder, without odor and with an earthy, metallic taste, almost insoluble in water and alcohol.

Unguentum Hydrargyri Ammoniati (U. S. P., B. P.), 10 per cent.

The white precipitate is not used internally and is more irritant than the oxides. The ointment is occasionally applied in skin diseases and to destroy parasites.

Liquor Hydrargyri Nitratis (U. S. P., B. P.), solution of mercuric nitrate, contains about 60 per cent. of the nitrate ($Hg(NO_3)_2$) along with about 11 per cent. of free nitric acid. It is a powerfully corrosive fluid which is used to cauterize the os uteri, cancers or condylomata. Symptoms of mercury poisoning have arisen from its application to the os uteri.

UNGUENTUM HYDRARGYRI NITRATIS (U. S. P., B. P.), citrine ointment, is used, diluted with oil or lard, in conjunctivitis, and also as an application to syphilitic sores and gangrenous ulcers.

Unguentum Hydrargyri Citratis Dilutum (B. P.).

A large number of new preparations of mercury have been introduced of late years and have received a more or less extensive trial, but have seldom been found to be superior to the older forms. Among these may be mentioned the *tannate*, which was introduced in the hope that it would cause less purgation than calomel, and might therefore be better adapted for the treatment of syphilis. 0.1–0.3 G. (2–5 grs.) in powder. The *carbolate, salicylate* (*either neutral or basic*), *benzoate, sozoiodolate, thymol-acetate* and many other similar compounds have been used instead of calomel for hypodermic or intramuscular injection, have each in succession been blazoned forth as the best preparation, and will probably be forgotten in the course of a few years. Several amino acid salts of mercury such as the *formamide*, the *amino-propionate* (alanin mercury) and the *succinimide* have been proposed as substitutes for corrosive sublimate in hypodermic injection. It was believed that the affinity of mercury for nitrogen being satisfied in these compounds, it would attack the proteins less, and as a matter of fact, the injections are said to be less painful than those of corrosive sublimate. *Colloid mercury* (*Hyrgol*) has been injected intramuscularly, but has no advantage over the older preparations.

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Fe essential to all living matter. Vertebrates mostly in blood. "Inorganic" r dissociable ~~giving~~ ppted by Amm. sulph & Prussian Blue test. Masked or organic do not (i.e. haemoglobin). Some between

I.e. chlorides, acetates, sulphates

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III. IRON.

Iron differs from the other heavy metals in being essential to the life of many, perhaps all, forms of protoplasm. In the vertebrates this is obscured by the fact that most of the iron is contained in the hæmoglobin of the blood, and its importance in the other tissues is generally ignored. In the invertebrates, however, in many of which no corresponding compound exists in the blood, considerable amounts of iron are found in the tissues, and there is no question that throughout the animal kingdom iron is essential to living matter, quite apart from its special relation to the blood in the vertebrates. Molisch has shown that it is also necessary for the development of the lower vegetable forms, and it has been found that in its absence the higher plants fail to form chlorophyll, although iron is not actually contained in the latter as it is in hæmoglobin.

The iron combinations are generally divided into two classes—inorganic and organic or masked.[1] In the former of these iron is contained in the ordinary salt form, is dissociated in solution, and can be recognized by such tests as the black precipitate with ammonium sulphide, and the blue precipitates with the ferrocyanide or ferricyanide of

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[1] "Organic" and "inorganic" are here used in a special meaning, and have no reference to the combination to which iron is attached, but to the method of attachment. Thus the acetate and albuminate of iron are both classified among the inorganic iron compounds, because they are capable of dissociation, and the iron is precipitated by ammonium sulphide. "Masked iron" is a preferable term for "organic iron," but has not been so widely used.

Fe pptt but does not corrode (unless acid constituent) proteins, not sol in liq so no penetration. No pptt by double salts, alb comp or organic Fe — unless previously decomposed. Large dose — G.I. irrit., emesis + purge. Prolonged — constipation + dyspepsia. Acid on teeth. Black is Fe tannate or S.

potassium. In organic iron these tests fail, or are only elicited after prolonged contact, as the iron ion is less readily dissociated. Examples of inorganic iron are the chlorides, acetates or sulphates, while the best type of organic ion is hæmoglobin, though numbers of others exist in the tissues. Between the ordinary salts of iron and hæmoglobin and its allies there exists a number of compounds which are stained black by ammonium sulphide after prolonged contact, and which it is impossible to class either as organic or inorganic.

When such a salt as the perchloride is added to a solution of protein, it precipitates it at once in the form of iron albuminate. This insoluble body is also formed in the living tissues when the perchloride is brought in contact with them, and forms a protective coating on the surface. Iron has no such relation to the proteins as mercury, and does not corrode them of itself, any destruction which may be caused by such compounds as the perchloride being due to the acid constituent and not to the metallic ion. The albuminate is not so flocculent as that of mercury, and tends to protect the tissues from the acid, so that the corrosion of iron compounds is limited to the surface. The double salts of iron, the albuminous compounds, and organic iron do not precipitate proteins, and are therefore neither irritant nor astringent as long as they maintain their original form and are not decomposed into simple salts.

Symptoms.—Inorganic iron compounds, of which the perchloride may be taken as a type, have an astringent, metallic, or often acid taste, but in ordinary doses induce no further symptoms. If swallowed in large quantities, they cause pain and uneasiness in the stomach, nausea, vomiting and often purging, with all the ordinary symptoms of acute gastro-intestinal irritation. General weakness and even collapse may be induced, but are manifestly secondary to the gastric and intestinal effects, and no symptoms which can in any way be attributed to the absorption of iron have been observed in either man or animals.

The prolonged use of inorganic iron is frequently followed by some dyspepsia and by constipation and colic, which are obviously due to the continued astringent action on the stomach and bowel. Other symptoms observed occasionally are blackness of the teeth and tenderness in the gums, which may be due to the acid contained in many iron preparations; the blackening of the teeth has been supposed to be due to the tannic acid of the food precipitating the inky black tannate of iron, or to the sulphide of iron being formed by the action of the hydrogen sulphide present in carious teeth. According to Buzdygan, the iron preparations increase the secretion of hydrochloric acid in the stomach, and may thus lead to hyperacidity, or aggravate it if already present. In artificial digestion, the salts of iron with organic acids are said to hinder the process more than those with inorganic acids, the ferric salts more than the ferrous, and the insoluble preparations least of all. The digestion of starch is almost unaffected by the presence of iron.

Intra ven = thrombosis. Kobert's [illegible] definite. No effect on circ. Spec action (irritant) on g.i. & kidney, probably on c.n.s. (weakness + paralysis) By mouth only local symp., as very slow absorption. What is ? increased haemoglobin formation

Iron given by the mouth induces leucocytosis (Pohl), and does not affect the amount of double sulphates excreted in the urine, so that it has no antiseptic action in the bowel (Mörner).

Some symptoms from the circulation are sometimes said to arise, but are for the most part subjective, and seem to be handed down by tradition rather than really observed. These are a feeling of congestion, fulness and heat in the head and hæmorrhages from the nose, throat and lungs, especially in phthisis. If these symptoms are not entirely imaginary, they are to be attributed to some reflex from the stomach and intestine and not to any direct action of iron on the heart or vessels.

When these astringent preparations are injected into the blood vessels in animals, they coagulate the proteins and cause thrombosis but no real symptoms of iron poisoning. Fatal thrombosis has been observed in patients from the injection of the perchloride into the uterus and also into nævi. The hypodermic injection of these salts causes some pain and swelling, but no further symptoms follow and the iron is found for the most part deposited in an insoluble form at the point of injection.

The **General Symptoms** of iron are obtained only by the intravenous injection of double salts, such as the tartrate of iron and sodium, which do not coagulate the blood and at the same time are capable of freeing the iron ion in the tissues. Such salts as the ferrocyanides or ferricyanides on the other hand leave the body unchanged, and the iron ion is not liberated, so that no iron symptoms are induced. Meyer and Williams found that the double tartrate caused in the frog slowness and clumsiness in movement, which gradually developed into complete paralysis of the central nervous system. The heart seemed to be little affected, but the skeletal muscles were somewhat less irritable than usual after death. In mammals the symptoms of iron poisoning were often very late in appearing, and began with some acceleration of the breathing, which later became slow and dyspnœic; vomiting and diarrhœa often followed and blood was sometimes seen in the evacuations of the stomach and bowel. Increasing weakness was followed by central paralysis and death, accompanied by weak convulsive movements. The heart seemed little affected, although the blood-pressure fell rapidly towards the end. Post-mortem, the mucous membranes of the stomach and intestine were found swollen and congested, and often contained numerous small blood extravasations. Kobert found that repeated injection of small quantities of the citrate of iron induces congestion of the kidney and the appearance of casts and albumin in the urine. In acute poisoning the alkalinity of the blood is reduced owing to the excess of lactic acid formed.

Iron, like the other heavy metals, would therefore seem to have a specific irritant effect on the intestinal and gastric mucous membrane, and to a less extent on the kidney. In addition, it depresses and eventually paralyzes the central nervous system, but it is impossible to state how far this is due to direct action and how far it is secondary to the action in the alimentary canal.

According to Kobert, iron perfused through the vessels has no effect on their calibre except in large doses, when it dilates them. The astringent action is due, therefore, to the precipitation of the proteins, and not to constriction of the vessels.

Apart from irritation of the stomach and intestine, no symptoms are induced by iron given by the mouth, because it is absorbed too slowly and in too small amount, and perhaps in a form which has little tendency to cause them.

The **Absorption of Iron** has been a subject of discussion only during the latter half of the last century, for up to that time it had been assumed that it passed into the tissues with comparative ease, and was there formed to hæmoglobin. In this way was explained its effect in anæmia, particularly in the form known as chlorosis, in which there is a deficiency of hæmoglobin rather than of blood cells. The benefit accruing from the use of iron salts in this disease has been attested by so many generations of physicians that only the most sceptical can have any doubt on the subject. The first to question this explanation of the action of iron in chlorosis was Kletzinsky, who formulated a theory of its action, which was soon forgotten, however, and only became popularly known when it was resuscitated by Bunge. This explanation, which is generally stated as Bunge's theory, has been widely held during the last few years, but has now been abandoned by almost all its former supporters, including its author, who has been compelled to admit not only that iron salts are absorbed but that their administration leads to an increased formation of hæmoglobin.

No account of the action of iron would be complete, however, without reference to an explanation which has at least had the effect of establishing a number of facts regarding the fate of iron in the body, and also the less desirable result of increasing to a considerable extent the number of patented preparations containing iron. Shortly stated, Bunge's theory is that in ordinary conditions a certain amount of iron is lost by the body constantly through the excretions, and this loss is made up by the absorption of the iron contained in the food. This food-iron consists wholly of organic iron, that is, of iron combined in such a way that sulphides attack it with difficulty; an example of such organic iron is the hæmatogen of the yolk of egg. In normal individuals the food-iron is sufficient to replace that lost by excretion, but in chlorosis the presence of large amounts of sulphides in the intestine causes the food-irons to be decomposed to ferric sulphide, which is insoluble and unabsorbable. When the ordinary inorganic iron preparations are administered in these cases, they are not taken up in place of the food-iron; but, by forming sulphide in the intestine, they remove the sulphuretted hydrogen and prevent the decomposition of the food-irons, which thus remain capable of being absorbed. Bunge and his followers went on to state that inorganic iron is never under any circumstances absorbed by the normal epithelium, but that when large quantities are administered, they tend to corrode the walls of the stomach and intestine, and are thus absorbed to some extent. Even then, however, they are incapable of being formed to hæmoglobin, the animal body being able to perform only the last steps of this synthesis after the plants have formed the simpler types of organic iron. This theory now possesses only historical interest, so that it is unnecessary to enumerate the arguments brought against it. It may be sufficient to state that if the ordinary preparations of iron acted only by binding the sulphides of the intestine, various other metals would be equally efficient in chlorosis; iron would not be beneficial injected hypodermically, and iron sulphide given so as to escape the action of the gastric juice would be equally useless. It is found, however, that no other metal can replace iron in chlorosis; that iron injected hypodermically is curative in chlorosis, and that the sulphide administered so as to reach the intestine unchanged acts as well as other preparations (Stockman). Finally, it has been shown that ordinary preparations of iron are absorbed.

disproving Bunge's theory.

Driven from their former position that inorganic iron is not absorbed by the intestine, the advocates of the use of organic iron in chlorosis have attempted to make a further stand by asserting that, although the ordinary preparations are absorbed, they are not used in the formation of hæmoglobin, llhosis. Fe normally in all tissues + secretions + food (1/12–1/8 gr) Same amt. ret in feces + urine. Increase ext via bowel – no increase in urine. May have been absorbed + excreted by bowel.

[illegible]) stored in spleen, then liver + bone marrow + mesenteric glands then excreted by caecum + large i

but after a more or less prolonged stay in the liver and other organs, are excreted. This statement is refuted, however, by several researches, in which the addition of inorganic iron to food deficient in iron (milk), or entirely free from it, prevented the anæmia which was observed in animals fed on the same food, but without iron. Finally Abderhalden, the latest exponent of Bunge's views, finds that inorganic iron increases the hæmoglobin of the blood, but suggests that it may do so indirectly by taking the place of the food-iron which supplies the needs of the tissues, the food-iron then being formed to hæmoglobin; he fails to supply any arguments in support of this theory, which it is therefore unnecessary to discuss.

The chief difficulties in following the course of iron in the body are due to its being present in all the tissues and secretions normally, and to the very small quantity which is contained in ordinary food, and which is essential to the maintenance of health. About 2½–3½ G. (40–55 grs.) of iron are estimated to be present in the tissues of a healthy human adult, the greater part of it existing in the form of hæmoglobin in the blood. Formerly it was believed that some 50 mgs. (1 gr.) of iron were taken in the food per day, but Stockman and Greig have recently shown that this estimate is much too high and that an ordinary dietary provides only about 5–10 mgs. (1/12–1/6 gr.) of iron per day; they found in one case that even 3–5 mgs. (1/20–1/12 gr.) were sufficient to preserve the iron equilibrium. About the same amount of iron is excreted per day, chiefly in the fæces, and to a much smaller extent in the urine.

When additional iron is supplied to the body, either as inorganic or as organic iron, much the greater part of it reappears in the stools. This does not necessarily entail that all of it has passed through the bowel unabsorbed, for iron is excreted through the intestinal epithelium, so that some of the iron of the stools may have been absorbed and reëxcreted. Probably none of that absorbed is excreted by the kidney, for even when a double salt is injected intravenously only a trace is found in the urine, and when it reaches the blood more slowly the proportion eliminated in this way falls. About 0.5–1.5 mgs. of iron are normally excreted in the urine in twenty-four hours, and the administration per os of iron preparations, whether organic or inorganic, does not affect this amount. The fact that an iron preparation given by the mouth does not increase the iron in the urine is therefore no evidence that it has not been absorbed.

Iron injected into the veins of animals is stored up in the liver, spleen and bone-marrow, but is taken up from these organs again, and is excreted by the epithelium of the cæcum and colon. When iron is given by the mouth, therefore, it may either pass along the canal and be thrown out in the fæces, or it may be absorbed, make a stay in the liver, be excreted in the large intestine, and again appear in the stools. The comparison of the iron in the food and in drugs with that of the stools therefore gives no clue as to how much has been absorbed and how much has simply passed through the intestine.

But the passage of iron from the liver to the intestine is a somewhat slow process, and it is therefore possible to detect the excess of iron in

Fe in bile not increased. Fe to chlorides in stomach then albuminates & absorbed by duod as such or as solids

the liver. This has been done repeatedly by the following method. Young animals of the same litter fed on milk have approximately the same amount of iron in the liver. If one be fed on milk only, the other on milk to which iron is added, the liver of the latter is found to contain more iron than that of the control. Other investigators have fed animals (rats or mice) on food that is practically free from iron, have killed them and estimated the iron in the whole body apart from the alimentary tract and compared it with that of animals treated in the same way except that iron was added to the food. The latter group contains much more iron than the control group fed on iron-free food, and in general presents a much more healthy and normal appearance.

Finally, attempts have been made to follow the iron in its course through the tissues. This is possible by the histological examination of tissues soaked in ammonium sulphide solution, in potassic ferrocyanide and hydrochloric acid, or in hæmatoxylin, as these form black or blue precipitates with most forms of iron, but leave the hæmoglobin unaffected. When animals are given iron preparations, and are then killed, and their organs stained by these reagents, the mucous membrane of the stomach and of the greater part of the small intestine gives no coloration, but the epithelium of the duodenum and the upper part of the jejunum is found to contain numerous granules of iron. These granules may be traced to the mesenteric lymph glands, are found in large numbers in the spleen around the corpuscles, to a much smaller extent in the liver, and in the cortex of the kidney. If, however, the animal be kept for some days after the iron is given, the reaction in the duodenum, spleen and mesenteric glands is less intense, while the liver gives much more distinct evidence of containing iron, and the epithelial cells of the large intestine and cæcum also give a strong reaction. This is interpreted to mean that iron is absorbed by the duodenum and is first stored in the spleen, but later finds its way through the blood vessels to the liver, where it rests again for some time, to be eventually taken up again by the blood and excreted into the large intestine and the cæcum. There is some question as to whether the lymph vessels are involved in the absorption of iron, and the most recent investigators have failed to find it in the thoracic duct, and accordingly hold that it is absorbed from the intestine into the blood vessels directly. The iron stored in the liver does not escape by the bile as might be anticipated. A small percentage of iron is a constant constituent of this fluid, but is not increased by iron given by the mouth or intravenously.

Nothing is known with certainty regarding the form in which iron is absorbed. It is assumed that in the stomach almost all the preparations form chlorides to a greater or less extent, are then changed into albuminates, and in this form pass into the duodenum, where they may be absorbed in solution, or may be precipitated and taken up as solids by the epithelial cells and the leucocytes. In the liver it seems likely that the absorbed iron is changed to hepatic fer-

In liver synthesized to ferratin, etc. Most Fe ingested not absorbed but in stools as sulphide + albuminate. Inorganic Fe same effect as food Fe. Increase Fe ingested, no increase in bile or urine.

ratin, and that it is stored in this form. Several other iron compounds have been found in the liver, and iron undoubtedly undergoes a number of synthetic processes there.

It must not be inferred from the foregoing that all of the inorganic iron swallowed is taken up by the intestinal epithelium. It is quite impossible to form even approximate estimates of the amount that is really absorbed and made use of by the tissues, but the probability is that only a small percentage is really taken up; the rest passing through the intestine and being thrown out in the stools. It is often stated that the iron stools are dark or black in color, from the sulphide present, but this seems to be seldom the case when they are passed, although they assume a darker gray or grayish black color in the air from oxidation. The iron is contained in them only to a small extent as the sulphide, some of the rest probably being albuminate.

To sum up what is known regarding the fate of the iron preparations, they are partially formed to the chloride and then to the albuminate in the stomach, pass into the duodenum, from which the great bulk is carried on into the lower parts of the intestine, while some is absorbed by the epithelium and leucocytes in solid form and perhaps in solution. It is then deposited in the spleen, where it may undergo some changes in form, is later taken up by the blood and deposited in the liver and perhaps in the bone marrow. Where the supply of iron has been inadequate for the formation of hæmoglobin, the originally inorganic iron is probably worked into higher forms and eventually into hæmoglobin in the liver, and it seems likely that ferratin is one of the intermediate steps in this synthesis. When there is no deficiency of iron for the formation of hæmoglobin, the liver slowly yields its store of iron to the blood, which carries it to the cæcum and large intestine, by the epithelium of which it is finally excreted. It is to be noted that the iron absorbed does not increase the amount of iron in the urine, bile or other excretions. The investigations on which this sketch is founded have been completed only in the last few years, and establish finally the truth of the position held by the older physicians and indeed by the clinicians of this later time also, that inorganic iron follows the same course in the tissues as food-iron.

But this explanation of the iron action does not cover all the difficulties of the case. Many cases of chlorosis recover without inorganic iron under hygienic conditions, such as rest, and particularly when foods rich in iron are prescribed, this being exactly what is to be expected on the theory that inorganic iron merely takes the place of the deficient food-iron. But many chlorotic patients show little or no improvement when treated with foods containing iron, even when there is no question that the iron supplied daily in food form is sufficient for the needs of the economy, and chlorosis even appears in individuals who have never suffered from any deficiency of food-iron. Yet many of these cases recover rapidly under inorganic iron. V. Noorden has attempted to explain this by supposing that inorganic

Inorganic Fe more efficient in chlorosis etc as more of it than food Fe & not bound up in colloids preventing absorption. Possibly specific stimulant to bone marrow & blood forming organs. Unabsorbed by unbroken skin, so baths n.g. in anemia.
Used: Chlorosis. Small doses at first, in non-astringent form.

Fe & aloes to overcome constipating effect & to help amenorrhoea. In anemias after typhoid hemorrhage, cachexia of malaria & syph.

iron when absorbed acts as a stimulant to the blood-forming organs, while food-iron has no such property. And some indications of abnormal activity of the bone-marrow cells have been observed in animals supplied with inorganic iron; this may not be the effect of stimulation in the ordinary sense of the word, however, for it may be explained by the unusual abundance of the materials necessary to their activity. The difference in the effects of the irons of the food and of the inorganic preparations may be due to the fact that food-iron is always accompanied by a large amount of colloid material, which may materially delay its absorption while inorganic iron on the other hand is much less completely enveloped, and may be more easily absorbed. In addition, the iron preparations are given in much larger amounts than the food-irons. When 10 mgs. (food-iron) are taken per day, only a small proportion (*e. g.*, 5 mgs.) may be absorbed, and this may be insufficient to supply the needs of the body, but if some hundreds of milligrams of inorganic iron be added, the proportion absorbed will be amply sufficient. The same effect might be obtained by the same amount of food-iron, but this is only to be obtained by giving more food than can be digested.

Iron is not absorbed from the unbroken skin and the iron and steel baths are therefore of no value in themselves in the treatment of anæmia.

Therapeutic Uses.—Iron is most frequently used in the treatment of **Chlorosis**, which in a large proportion of cases recovers entirely under it. Some cases, however, improve somewhat under iron, but relapse when it is left off, and a certain number of patients show no improvement whatever under it. These last are not generally regarded as suffering from chlorosis proper, but from a more malignant form of anæmia. A number of symptoms which are due to chlorosis, and which are often more prominent than the original disease, are also relieved or entirely removed by iron. Thus gastric catarrh, amenorrhœa, or œdema may disappear under it, but in these cases the symptoms are chlorotic in origin, and the improvement is due to the increased hæmoglobin, and not to the direct action of iron on the stomach, uterus or circulation. In chlorosis the iron is generally given in small doses, at any rate at first, and the less astringent preparations are preferred by most clinicians, although some still advise the perchloride. When chlorosis is complicated with gastric catarrh, some authorities advise that the latter be treated before the general condition, as iron in itself is liable to irritate the stomach. In many cases, however, the catarrh is secondary to the chlorosis, and can only be treated successfully by improving the condition of the blood; the iron preparation here ought to be mild and not irritating. In chlorosis the tendency to constipation may be increased by iron, and a purge is often required, such as the iron and aloes pill, which is particularly recommended when chlorosis is attended by amenorrhœa.

Iron is of less value in other forms of anæmia, although it is often

Contra in gastric catarrh & fevers. .1–.2 G, 3× day.
Astringents & Styptics ([illegible]) – Fe alb, not fibrin · nose gums tooth extraction

prescribed and may be followed by some improvement. Thus it may be administered during convalescence from acute disease, such as typhoid fever, or nephritis, and in the anæmia induced by profuse hæmorrhage iron often seems to accelerate the recuperation of the blood. It is often prescribed for the cachexia of malaria, syphilis and other chronic diseases.

Iron is said to be contraindicated where there is fever, in plethoric individuals with a tendency to hæmorrhages, and in some forms of heart disease. In these conditions the iron preparations can harm only from a reflex induced from the stomach, as the small quantity of iron absorbed is incapable of producing any effects in the tissues. In phthisis it is very generally credited with causing hæmorrhage from the lungs, but it may be questioned how far this apprehension is based on observation, and how far it is a relic of old and forgotten theories of the action of iron. It has to be given with caution here in order to avoid irritation of the stomach and dyspepsia, and in the presence of gastric catarrh from any cause, its effects have to be watched carefully.

Some of the older authorities advise iron to be given in large quantities, but the dose has been reduced of late years to about 0.1–0.2 G. (2–3 grs.) three times a day. It is given after meals in order to avoid the irritant action on the stomach as far as possible. It is to be noted that on giving 0.1 G. of iron three times a day, about thirty times as much iron is given as is required normally in food, so that the chlorotic receives more iron per day than a workman in a month.

Iron is occasionally injected hypodermically, with the object of avoiding the irritation of the stomach, but this procedure is painful and causes some swelling and irritation, which lasts twenty-four hours or more. Most of the salts are precipitated at the point of injection, but some, such as the citrate, are taken up by the blood at once; the danger of renal irritation, anticipated by Kobert, does not seem to arise if small quantities are used; 1–2 grs. are injected in 5 per cent. solution daily.

Iron has been recommended in erysipelas, but has proved valueless in the hands of most investigators. Some of the iron salts are employed as **Astringents**, the most popular preparations for this purpose being ferrous sulphate, which has been used to some extent in diarrhœa, and also externally. The perchloride is perhaps the best **Styptic** of its class. When applied to a bleeding point, it precipitates the proteins of the blood plasma, and thus forms an obstruction to the flow of blood similar to that caused by clotting, although no fibrin, but only a mass of iron albuminate, is formed by the perchloride. This styptic action is of value in capillary and recurrent hæmorrhage, while in bleeding from an artery, the ordinary surgical methods are of course preferred. The chloride arrests hæmorrhage only when it can be brought into actual contact with the bleeding point, and where this is covered by a large mass of semicoagulated blood, the treatment is of no avail, as it simply forms the albuminate with the blood with

Valueless in hemorrhage of int. organs + in ppt alb in albuminuria + nephritis.
$FeSO_4$ as disinfectant for sewage.
Tinct ferri chloridi (0.5 cc. ± chlorosis). As gargle attacks teeth

which it comes into contact first, and this may be far from the actual point of rupture. As an application to the stomach and bowel in hæmorrhage from these parts, the perchloride is unlikely to prove successful, while in bleeding from the nose, or gums, or after the extraction of a tooth, it is more reliable. It has been injected into the uterus in hæmorrhage, into nævus in order to cause coagulation and subsequent cicatrization of the tissue, and into aneurysms. This is a very dangerous treatment, however, for several cases of fatal embolism have arisen from the precipitated albuminate being carried off in the veins. Perchloride of iron solution has been sprayed into the air passages in hæmoptysis, but if sufficiently concentrated to coagulate the blood at the bleeding point in the lungs, it would certainly induce irritation and coughing. The perchloride is, of course, valueless in hæmorrhage from internal organs, for in the first place, very little of it is absorbed, and in the second place, what does pass into the tissues is already in protein combination, and therefore incapable of coagulating the blood. The same objection applies to the alleged astringent effect of iron in nephritis. It is possible that iron may lessen the albumin in the urine in these cases, although the clinical evidence is contradictory on the subject, but it is absolutely certain that it does not do so by any local action on the albumin in the kidney.

The sulphate of iron is used as a disinfectant for sewage. It acts here merely by precipitating the proteins, which carry down the bacteria mechanically. The proteins of the sewage may be increased by the addition of blood before the sulphate is applied. The sulphate of iron is used, because it is cheaper than the other salts of the heavy metals.

PREPARATIONS.

Ferri Chloridum (U. S. P.), ferric chloride ($Fe_2Cl_6 + 12H_2O$), orange yellow crystals, with a strong astringent taste, very deliquescent in air, soluble in water and alcohol. 0.065 G. (1 gr.).

Liquor Ferri Chloridi (U. S. P.), a solution of ferric chloride containing 29 per cent. of the anhydrous salt or about 10 per cent. of iron.

TINCTURA FERRI CHLORIDI (U. S. P.) contains 13.28 per cent. of ferric chloride. 0.5 c.c. (8 mins.). chlorosis 0.5 cc.

Liquor Ferri Perchloridi Fortis (B. P.) is formed by dissolving iron in hydrochloric acid and contains 22½ per cent. of iron. It is an orange-brown fluid, with a strong astringent taste.

Liquor Ferri Perchloridi (B. P.) and

TINCTURA FERRI PERCHLORIDI (B. P.) are formed by diluting the strong liquor with three times as much water, and with two parts of water and one of alcohol respectively. 5–15 mins.

The chloride is used as a styptic either as the Liquor Fortis (B. P.) or in a very much stronger form, prepared by allowing the crystals to deliquesce. A plug of cotton-wool steeped in the solution is used to stop bleeding after the extraction of teeth, and the liquor has been injected into the uterus in hæmorrhage and into aneurisms and nævi. When diluted it may be used as a gargle, but has a disagreeable, inky taste, and attacks the teeth. The tincture is very commonly used in the treatment of chlorosis. It ought to be taken in a glass of water, and through a quill or glass tube, in order to avoid injury to the teeth.

Ferri Sulphas (U. S. P., B. P.), ferrous sulphate ($FeSO_4 + 7H_2O$), large, pale, bluish-green crystals with a saline, astringent taste, soluble in water, insoluble in alcohol and unstable in moist air. 0.05–0.3 G. (1–5 grs.).

Ferri Sulphas Granulatus (U. S. P.), recrystallized ferrous sulphate in very small crystals. 0.2 G. (3 grs.).

Ferri Sulphas Exsiccatus (U. S. P., B. P.), dried ferrous sulphate ($2FeSO_4 + 3H_2O$), ordinary sulphate from which most of the water of crystallization has been driven off by heat. A grayish-white powder resembling the ordinary sulphate in its solubility. 0.03–0.2 G. (½–3 grs.).

✓ astringent garg 0.2cc

Liquor Ferri Subsulphatis (U. S. P.), Monsel's solution, an aqueous solution of basic ferric sulphate of variable chemical composition and containing about 13.6 per cent. of metallic iron. 0.2 c.c. (3 mins.). Used as an astringent gargle and in general like the chloride.

Ferri et Ammonii Sulphas (U. S. P.), ammonio-ferric sulphate or ammonio-ferric alum ($Fe_2(NH_4)_2(SO_4)_4 + 24H_2O$), is a double salt forming pale violet crystals with an acid astringent taste—soluble in water, not in alcohol, 0.5 G. (7½ grs.).

The sulphate of iron is very astringent, though less so than the ferric salts. It is used as an astringent application to mucous membranes, such as the eye, mouth, urethra, more rarely internally in anæmia, although it is less irritant than the chloride.

The *Pil. Aloes et Ferri* (U. S. P., B. P.), which is used very largely in amenorrhœa and in chlorosis with constipation, contains dried sulphate of iron. Dose, B. P., 4–8 grs.

Ferrum Reductum (U. S. P.), **Ferrum Redactum** (B. P.), reduced iron, a very fine, grayish-black, lustreless powder, without taste, insoluble in water or alcohol, soluble in acid. It consists of metallic iron, with a small amount of the magnetic oxide. 0.05–0.3 G. (1–5 grs.).

Trochiscus Ferri Redacti (B. P.), each contains 1 gr. of reduced iron.

Freshly prepared.

Ferri Carbonas Saccharatus (U. S. P., B. P.), saccharated ferrous carbonate, is formed by precipitating ferrous sulphate with sodium bicarbonate (ammonium carbonate, B. P.), washing the precipitate and adding sugar. It contains ferrous carbonate along with some ferrous sulphate and sodium bicarbonate (U. S. P.), and is a greenish-brown powder, which rapidly oxidizes in the air, and has a sweetish, astringent taste. The carbonate is a very unstable body and on keeping is slowly transformed to ferric hydrate ($Fe_2(OH)_6$). The sugar is added in order to retard this oxidation, but the carbonate ought not to be dispensed unless it is of recent preparation. 0.2–1 G. (3–15 grs.).

Prepare freshly 0.065-2 pills

Pilulæ Ferri Carbonatis (U. S. P.), **Pilula Ferri** (B. P.) ferruginous or chalybeate pills, **Blaud's Pills**, are prepared in the same way, by the action of ferrous sulphate and carbonate of potash or soda. Sugar, tragacanth and glycerin are added; they ought to be freshly prepared in order to avoid the formation of the hydrate. Each pill (U. S. P.) contains about 0.06 G. (1 gr.) of iron, that is, 5 grs. contain about 1 gr. 2 pills U. S. P., 5–15 grs. B. P.

Massa Ferri Carbonatis (U. S. P.), Vallets' Mass, is formed by the action of ferrous sulphate and sodium carbonate. Sugar and honey are added to the precipitate to form a mass of the proper consistency for pills. This preparation has never enjoyed the popularity of Blaud's pills and is superfluous. 0.25 G. (4 grs.).

Prepare freshly 15-30cc

Mistura Ferri Composita (U. S. P., B. P.), Griffith's mixture, is formed by mixing ferrous sulphate, potassium carbonate, myrrh, sugar, spirits of lavender (nutmeg, B. P.) and rose water. The ferrous carbonate ($FeCO_3$) is precipitated and the mixture has therefore to be shaken before taking, and ought to be freshly prepared. 15–30 c.c. (½–1 fl. oz.).

Reduced iron and the four ~~carbonate~~ preparations are used exclusively in the treatment of anæmia. They are practically devoid of irritant properties.

and are among the best of all the iron preparations for this purpose. The Blaud's Pills have in particular a well merited reputation in the treatment of chlorosis and of chlorotic amenorrhœa. Another preparation used for this purpose but not official is *Ferrum Dialysatum* in which a considerable amount of iron oxide is kept in a semi-colloid state dissolved in a minimum amount of the chloride. It tastes of iron but is not astringent.

Ferri Hydroxidum (U. S. P.), ferric hydrate, or hydroxide ($Fe(OH)_3$), and *Ferri Hydroxidum cum Magnesii Oxido* (U. S. P.) are used almost exclusively in the treatment of arsenic poisoning, 120 c.c. (4 fl. oz.). The remedy is harmless in itself, but its efficacy is very doubtful.

As poison?
12 cc.

Ferri Citras (U. S. P.), transparent, garnet-red scales with a slight iron taste. 0.25 G. (4 grs.).

Ferri Phosphas Solubilis (U. S. P.), *Ferri Pyrophosphas Solubilis* (U. S. P.). These insoluble salts are rendered soluble by the presence of sodium citrate—thin, green scales with a saline taste. 0.25 G. (4 grs.).

Ferri Hypophosphis (U. S. P.) ($Fe(PH_2O_2)_3$), a white powder, odorless and nearly tasteless, almost insoluble in water, but dissolved by solutions of the alkali citrates. 0.2 G. (3 grs.), in pill.

Pilulæ Ferri Iodidi (U. S. P.), each contains 0.04 G. of iron. 2 pills.

Syrupus Ferri Iodidi (U. S. P., B. P.) contains about 5 per cent. of the iodide U. S. P., 10 per cent. B. P. 2–4 c.c. (½–1 fl. dr.).

These preparations have all been prescribed to a greater or less extent in the treatment of anæmia. The iodide has been advised in order to combine the effects of iodide and iron, but the iodide given in this form is in much smaller quantity than that found necessary in the iodide of potassium treatment, and it seems open to question whether the improvement is not due to the iron only. The hypophosphite is superfluous.

Ferri et Quininæ Citras (U. S. P., B. P.), thin scales of a reddish-brown color, and of a bitter, iron taste, slowly soluble in water, partially soluble in alcohol, containing 11.5 per cent. of quinine and 13.5 per cent. of iron U. S. P. 0.2–0.6 G. (3–10 grs.).

Ferri et Quininæ Citras Solubilis (U. S. P.), thin scales of a greenish color and of a bitter, iron taste, easily soluble in water, only partially in alcohol. It contains the same amount of iron and quinine as the ordinary preparation. 0.25 G. (4 grs.).

Ferri et Strychninæ Citras (U. S. P.), thin, transparent scales of garnet-red or yellowish-brown color, readily soluble in water, containing about 1 per cent. of strychnine and about 16 per cent. of iron. 0.12 G. (2 grs.).

Syrupus Ferri, Quininæ et Strychninæ Phosphatum (U. S. P.), *Syrupus Ferri Phosphatis cum Quinina et Strychnina* (B. P.). 2–4 c.c. (½–1 fl. dr.).

Glyceritum Ferri, Quininæ et Strychninæ Phosphatum (U. S. P.), 1 c.c. (15 mins.).

Elixir Ferri, Quininæ et Strychninæ Phosphatum (U. S. P.). 4 c.c. (1 fl. dr.).

Ferri et Ammonii Citras (U. S. P., B. P.), thin garnet-red scales with an acid, iron taste, soluble in water and containing 16 per cent. iron. 0.2–0.6 G. (3–10 grs.).

Ferri et Ammonii Tartras (U. S. P.), thin, transparent, garnet-red scales, very soluble in water and containing about 13 per cent. of iron. 0.25 G. (4 grs.).

Ferri et Potassii Tartras (U. S. P.), *Ferrum Tartaratum* (B. P.) resembles the last preparation, but contains about 15 per cent. of iron. 0.25 G. (4 grs.).

Liquor Ferri et Ammonii Acetatis (U. S. P.), Basham's mixture, contains only a very small proportion of iron, along with acetic acid, ammonium acetate, aromatic elixir and glycerin. 16 c.c. (4 fl. drs.).

Vinum Ferri (B. P.). 1–4 fl. drs.

Vinum Ferri Amarum (U. S. P.). 8 c.c. (2 fl. drs.). 8cc.

[illegible] inorganic Dose .5 to 1.5 G. Blood & haemoglobin in stomach ⇒ haematin & absorbed.

Vinum Ferri Citratis (B. P.), *Vinum Ferri* (U. S. P.). 4–15 c.c. (1–4 fl. drs.).

The two wines of iron of the U. S. P. are practically identical except that the first contains the citrate of iron and quinine, the second the citrate of iron and ammonium. Each is made up with tincture of sweet orange peel, syrup and white wine. The iron wine of the B. P. is formed by dissolving iron in sherry wine, the citrate of iron wine by dissolving the citrate in orange wine.

The double salts of iron (scale preparations) and the wines are used to some extent in chlorosis, but more frequently in convalescence from acute fevers, which is often attended by anæmia; in these cases the iron wines are often of considerable value. The double salts are not so liable to disturb the digestion as the other soluble preparations of iron, but are not superior to the carbonate preparations and the reduced iron in this respect.

Iron is contained in many *mineral waters,* which are therefore advised in cases of anæmia. It is generally in the form of the carbonate, which is dissolved by the excess of carbonic acid present, but becomes oxidized to the insoluble ferric hydrate in the air. The amount of iron contained is small, seldom being more than 0.1 G. per litre, but the treatment of chlorosis is unquestionably aided by change of scene and in particular by the high elevations at which many of these springs are situated, so that the success of treatment with these iron waters is perfectly intelligible. Bathing in iron water has no further action on the blood than ordinary baths, as no iron is absorbed.

Many **Protein Compounds** of iron, such as the *albuminate* and *peptonate,* have been introduced into therapeutics, but possess no advantage over the usual preparations, which they resemble in their reactions to sulphide and other tests. Schmiedeberg found in the liver an iron compound, *ferratin,* which would seem to stand midway between the ordinary dissociable salts and hæmoglobin, for it reacts to ammonium sulphide more tardily than the former, while the latter is not affected by this reagent. Artificial ferratin, formed from white of egg, is not identical with this hepatic ferratin and is decomposed in part in the stomach into ordinary salts. It is not found to be superior clinically to the other milder preparations of iron. Dose, 0.5–1.5 G. (8–20 grs.) per day, in powder or pill or in solution as a sodium compound.

Blood has been used in therapeutics by uncivilized peoples since time unknown, and has also been recommended in modern medicine in the treatment of chlorosis, in which it is administered by the mouth, and also hypodermically, though the latter method is difficult to carry out aseptically. *Hæmoglobin* has also been advertised largely of late years in a more or less impure form. In the stomach, hæmoglobin, whether contained in blood or as crystals, is changed to hæmatin; Abderhalden found that both hæmoglobin and hæmatin are absorbed and lead to an increase in the hæmoglobin of the blood.

On the whole, these new iron preparations have little to recommend them as superior to the older ones and are therefore superfluous.

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Dense heavy ppt - fine astringent. Less irrit. as insol salts with [illegible] H_2SO_4
Nitrates sol. + corrosive. Acetates used = only slightly corrosive = sugar of lead = astringent
sweet taste + constipation

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IV. LEAD.

Lead is used to some extent in therapeutics, but its chief interest from a medical point of view lies in the frequency with which it gives rise to chronic poisoning, and in the diversity of the symptoms presented in that condition.

Solutions of lead salts precipitate albumin, and the precipitate is more dense and heavy than that of mercury, and less soluble in excess of the salt. This precipitate is formed when lead solutions are applied to the mucous membranes, and protects them from the penetration of the metal, so that lead is one of the least corrosive, and one of the most astringent of the heavy metals. This absence of corrosion is only in part due to the character of the precipitate, for lead forms insoluble and therefore non-irritant salts with two of the most corrosive acids, hydrochloric and sulphuric acids. The soluble nitrate of lead is comparatively irritating because it is readily dissociated and also because the nitric acid formed by its contact with protein is itself corrosive. The only soluble salts which are largely used are the acetates, and these are slowly dissociated and the acid is only slightly active, so that the astringent metallic ion alone comes into play.

Symptoms.—In ordinary therapeutic doses, the acetate of lead (sugar of lead) has a sweetish, metallic taste followed by a feeling of astringency, and induces no symptoms except constipation. The stools after lead are often said to be dark in color from the sulphide formed in the intestine, but this does not seem to be the general rule. Probably little lead is absorbed from an ordinary dose of the acetate; at any rate no symptoms arise from the general action of the metal absorbed.

Lead acetate solutions applied to the skin have no effect, but mucous membranes, or exposed tissues, such as ulcers, are covered with a thin not ppt on skin. ppt on m.m. & ulcers. large amts = usual g.i. sym. little absorbed suddenly. Chronic - repeated doses by stomach or lungs. stored long in liver & kidney, slowly excreted by, urine, bile, intest epith, milk, saliva

pellicle of albuminate, which serves to protect them from irritation, and thus promotes their healing.

When very large quantities of acetate are swallowed, particularly if in a concentrated form, they give rise to the ordinary symptoms of irritant poisoning, nausea, vomiting, pain in the abdomen, violent purging or sometimes constipation, blood in the vomited matter and stools, great thirst, weakness, and collapse. In some instances in which the patients recovered from these symptoms, they subsequently suffered from chronic lead poisoning, but apart from these, nothing in the course of acute lead poisoning suggests the absorption of the metal, all the symptoms being obviously due to the local effects on the stomach and bowel, and to the consequent collapse. In fact the effects of a sudden absorption of lead in man are unknown.

In animals also, some difficulty has been met in inducing the symptoms due to the action of large quantities of lead in the tissues, because most forms of lead injected into the vessels precipitate the proteins of the blood and cause embolism, while, on the other hand, only local symptoms can be induced by its administration by the mouth. Harnack injected salts of lead-triethyl, in which the metal is not contained in a dissociable form, but which is decomposed in the tissues and then gives rise to lead symptoms. In the frog it induced general paralysis, apparently from direct action on the central nervous system. The frog's muscle is also affected by lead as is shown by changes in its elasticity and irritability and by changes in the form of the curve of contraction (Cash). In the dog large doses of lead injected into a vein induce weakness and paralysis, violent diarrhœa and colic, chorea-like movements, tremors, which often assume the appearance of true convulsions, and ataxia. The diarrhœa Harnack found to be due to violent contractions of the intestinal walls, which maintained a certain degree of contraction even when no peristaltic wave was passing. This action of lead upon the intestine is of interest, because it bears a close relation to the colic observed in chronic lead poisoning in man, although here there is generally constipation, and also because it connects lead with the other heavy metals, all of which have more or less specific action on the intestine. The ataxia and other brain symptoms also have their counterpart in the brain symptoms of chronic poisoning in man.

A single dose of a lead salt does not generally give rise to any symptoms which would indicate the absorption of the metal, but the continued ingestion of small quantities by way of the stomach, or by inhalation by the lungs, induces chronic poisoning, which can be explained only by its absorption. There seems some reason to believe that lead is absorbed from the unbroken skin, though it is possible that some of the metal was carried to the mouth and swallowed with the food in the cases on which the statement is founded. Lead is apparently **Absorbed** more rapidly than most of the metals except mercury, and remains lodged in the tissues a long time, the excretion taking place only very slowly. It is found in most organs in cases of poisoning, particularly in the liver and kidney. It is **Excreted** in the urine, the bile, the secretion of the intestinal epithelium, in the milk and saliva, and in traces by the skin glands.

Chronic Lead Poisoning is the commonest of all forms of metallic poisoning, and at the same time one of the most insidious. It is al-

Weakness + anæmia & previous attack predispose
A trade disease, in prep + canning of foods etc. May affect 1 organ or whole body

du morgen

ways accidental, and although it is most common in workers in lead, may occur in persons who are not apparently liable to come in contact with the metal. There is no question that some people are much more susceptible to lead than others. Anæmia and weakness from any cause are generally believed to predispose to the disease, women and children are more liable to it than men, and alcoholism and previous lead intoxication increase the tendency to the attack. Relapses are very common, and may occur years after the first symptoms, even although there has been no further exposure in the interval. Lead smelters, workers in white lead factories, painters, plumbers, electricians, and typesetters are liable to lead poisoning from continually handling the metal; but other trades are not exempt from it, and sometimes the channels by which it gains entrance to the body are very obscure. Some of the more common causes of poisoning are lead water-pipes or cooking utensils, lead used to close tins of meat or fruit, and lead in hair dyes. Formerly a common source of poisoning was wine and cider to which lead had been added to reduce the acidity. A considerable number of cases of poisoning have been recorded from the use of lead preparations as abortifacients.

The symptoms of chronic lead poisoning vary greatly in different cases, sometimes only one or two organs being attacked, in others the whole economy appearing involved in the disorder. The symptoms may be divided into groups for convenience, but it is to be noted that many of these appear to be closely inter-connected, and that in many cases it is impossible to decide whether a set of symptoms is due to direct action upon a single organ, or to the simultaneous disease of several.

The **Mouth, Stomach and Digestion** very often give early indications of lead poisoning. The patient complains of loss of appetite, nausea, constipation, wasting, a metallic taste and fœtid breath, and a blue-black line is seen along the margin of the teeth where they enter the gums. This "lead line" is due to the precipitation of lead sulphide by the hydrogen sulphide produced by the action of bacteria, and it is often absent, especially where the teeth are not carious and are kept clean. The metallic taste seems due to the excretion of lead in the saliva, and the loss of appetite may arise from the same cause. These symptoms may be produced in animals also. Virchow and Maier found in one case in man the gastric epithelium in a state of fatty degeneration, and proliferation of the connective tissue of the mucous membrane.

Another early symptom is **Anæmia**, which may be due in part to malnutrition, but is attributed mainly to an abnormal destruction of the red cells of the blood; the white corpuscles are increased in many cases but not in all. It is often accompanied by jaundice, with the highly pigmented urine and other symptoms which usually follow the liberation of large quantities of hæmoglobin from the breaking up of red cells. It is stated that the red blood-cells often contain granules staining with basophile dyes and indicating incomplete disappearance

[illegible]
days or weeks, disappears, may return. Very acute pain. Spasm of intest. = bp. up, pulse slow
palsy of extensors = finger then wrist drop. Contracture of flexors = claw hand
due to degeneration of the nerves, peripheral neuritis, extends to ant. horn cell.

of the nucleus; this change may present itself before any other symptom. The anæmia is often very marked, and is sometimes the chief or only symptom of lead poisoning; according to some authorities, it is present in a greater or less degree in the majority of white-lead workers, and it leads to weakness, languor, and in young women often to amenorrhœa. Abortion is very often met with in lead poisoning, and in women employed in lead works who do not show any marked symptoms of disease. The children of parents suffering from lead are often weak and undersized, and a very large proportion of them die in early infancy.

One of the commonest symptoms is **Lead Colic**, painters' colic, colica saturnina or colica Pictonum. This generally sets in suddenly, and is accompanied in most cases by obstinate constipation, in a very small proportion by diarrhœa. Paroxysms of the most acute agony are followed by intervals of comparative freedom from pain, but in these intervals some tenderness of the abdomen may be complained of, while during the attack pressure generally relieves the pain. The colic lasts for several days, or a week, and then disappears, but is liable to return at intervals. The abdomen is generally hollow, retracted and hard, and during the acute spasms the patient often gains some relief by lying on his face with the fists pressed against the umbilical region, to which the pain is usually referred. Vomiting is frequently present, the pulse is slow and very hard, especially during the acute crises, while the respiration may be accelerated. The urine is scanty, and, according to Stokvis and Nakorai, contains hæmatoporphyrin.

The cause of lead colic is evidently spasm of the intestine, but it is uncertain whether it arises from action on the muscle or on the ganglionic plexus. It can be induced in animals, and according to Harnack, is relieved by atropine. The blood-pressure is raised in man, not only during the spasms, but also in the intervals. This contraction of the vessels and the slowing of the pulse is often said to be reflex from the pain, but this seems to be disproved by the fact that it remains during the intervals. Some writers have therefore regarded the colic and its attendant symptoms as due to a vascular spasm, and have supported this by showing that nitrite of amyl, which dilates the vessels, also relieves the colic.

Another common result of chronic lead poisoning is **Paralysis**, lead or painters' palsy, paralysis saturnina, which is almost invariably limited to certain groups of muscles, the extensors of the forearm. It is bilateral in the great majority of cases, but sometimes involves only one arm. The affection generally begins in the middle and ring fingers, which cannot be extended, then spreads to the index and little finger, and afterwards to the thumb and wrist. The fingers remain flexed and later the wrist is similarly affected, so that the condition is often known as wrist-drop. Even after all the other muscles of the extensor surface of the forearm are involved, the supinator longus remains normal as a general rule. The muscles affected atrophy

Afferents apt to be affected before efferents - hence anaesthesia.
Arthralgia = boring pains of joints. Rarely amblyopia or blindness (neuritis of II)

rapidly, and in old cases contracture of the flexor muscles sets in, when the limb becomes immovable and has a characteristic claw-like appearance. More rarely other regions are affected, such as the laryngeal muscles (in the horse), the external rectus of the eye, or the muscles of the leg. In rabbits and guinea-pigs several observers have succeeded in inducing paralysis of the hind limbs, and the legs are said to be affected very often in young children. When paralysis is complete, the induced electric current fails to cause contraction, whether it is applied to the muscles or to the nerve, but the galvanic shock induces an abnormally strong contraction when it is passed through the muscle, the make shock having more effect than the break; the contraction is more prolonged, the relaxation slower than in normal muscles. This reaction of degeneration is said to occur in the other muscles in lead poisoning, even when no paralysis can be detected in them. The cause of lead palsy is peripheral neuritis and degeneration of the nerves, which sometimes involves secondarily the cells of the anterior horn of the spinal cord. Peripheral neuritis and paralysis have been elicited repeatedly in animals. The affection of the efferent fibres by the poison more commonly gives rise to symptoms than that of the afferent fibres, but these are also involved in the action, as is shown by local **Anæsthesia.** This is generally sudden in its onset, but may be preceded by numbness or tickling of the skin, and generally lasts only one or two weeks when sensation returns again to the part.

Lead **Arthralgia,** which arises from the same action on the peripheral nerves, is more commonly observed, perhaps because it is so much more evident. It consists in sharp lancinating or boring pains around the joints, the intensity of the pain being comparable only to that of lead colic. It sets in suddenly, usually in the night, and generally disappears as suddenly.

Lead **Amblyopia,** or blindness, is one of the rarer affections. The sight may be lost completely, or may only be dim, and the onset may be sudden or gradual. It arises from neuritis of the optic nerve and degeneration of the retinal nerve cells, or in some cases may be the result of the changes in the kidney occasioning albuminuric retinitis or effusion into the optic sheath. The sudden cases of blindness are probably due to uræmia, and the prognosis in all forms depends on the duration of the neuritis, and, in the case of albuminuria, on the extent to which the kidney is involved. In early cases of neuritis, the disease can generally be arrested and even complete restitution may take place, but if it be neglected, optic atrophy follows.

Under saturnine **Encephalopathia,** a number of disorders of the brain are classed together. They are comparatively rare at the present time, and their onset generally indicates long standing and neglected lead intoxication, although in some cases the patient has been shown to be exposed to the poison for only a short period. One of the most characteristic features is the rapidity with which the disease changes from one type to another, and the diversity of the symptoms present

Varied & rapidly changing cerebral signs - headaches, vertigo, insomnia
deafness, stupor, weakness, tremor, delirium, coma etc. etc. Direct action
on the brain cells. Insidious
Spec. on kid.: typical red granular nephritis - dropsy, uraemia, amblyopia. Urine under low sp. g.
Predisposes to gout.

at one time. These cerebral symptoms sometimes appear suddenly, while in other cases they are heralded by violent headache, giddiness and sleeplessness, or by amblyopia, deafness, great depression, stupor, weakness and tremor. Later, sudden mania and delirium, with convulsions resembling chorea or epilepsy, hallucinations and illusions indistinguishable from those of alcoholic delirium, sudden apoplectic paralysis, ataxia, partial analgesia, hyperæsthesia, or coma may occur separately or in succession. Oliver states that the encephalopathic symptoms are especially liable to occur in persons addicted to alcohol.

In animals cerebral symptoms are readily induced by lead, either by intravenous injection (Harnack), or by chronic poisoning with the ordinary salts. Chorea, tremors and general convulsions have been caused in this way in dogs.

The encephalopathia is obviously of cerebral origin for the most part, although the lower divisions of the central nervous system are also involved in many cases. In several autopsies of patients dying from lead poisoning, atrophy of parts of the cerebrum, or hæmorrhages have been found, and very frequently disease of the brain vessels has been met with. In other cases of undoubted encephalopathia in man, no such lesions have been observed, and in animals poisoned by Harnack's method they are certainly not present. Many of the symptoms are obviously not due to these gross lesions, for the suddenness of their onset and of the recovery precludes any such explanation, and shows that lead has also a direct action on the brain cells.

It must be noted that in addition to these generally recognized symptoms of encephalopathia saturnina, several obscure chronic nervous diseases have been ascribed by Putnam and others to lead intoxication, and it is certainly possible that its action may prove to be even more wide-reaching and insidious than is generally recognized at present.

Another organ acted on by lead, especially in prolonged poisoning, is the **Kidney,** which is often found to present a typical red granular nephritis. During life the urine presents the ordinary appearances of this disease, being copious in amount and of low specific gravity, and containing comparatively small quantities of albumin or casts. In some cases in man, the kidney has presented a mixture of parenchymatous and interstitial disease, while in animals the parenchyma alone is affected, perhaps because the experiments have not lasted long enough. The disease of the kidney from lead poisoning, as from other sources, may cause dropsy, uræmia and amblyopia, but it is to be noted that the brain and eye may be affected in cases in which there is no nephritis.

Gout is very common in lead poisoning, which evidently predisposes to this disease, if it does not actually cause it, for Garrod states that in one-fourth of the cases of gout treated by him there was a history of lead poisoning. In districts where ordinary gout is rare, lead

Anemia, renal cond + direct action predisposes to arteriosclerosis
So acts on many diff tissues + differently.

In course

poisoning seldom leads to it, but where ordinary gout is met with, it is a fairly common complication of saturninism. or lead

Another condition in which lead poisoning may act as a predisposing factor is **Arteriosclerosis**; the malnutrition, anæmia, and renal changes induced by the metal would in themselves tend to induce changes in the vessels throughout the body, and degeneration of their walls is met with in a considerable proportion of cases of very prolonged exposure to it.

Lead poisoning runs no definite course. As a general rule the anæmia, wasting, constipation and weakness appear early, and then colic may follow, or paralysis, or arthralgia. Nephritis, encephalopathia, anæsthesia and gout are rarer, and as a rule only occur in very prolonged poisoning. Any one of these symptoms may be present alone, and the diagnosis is then very difficult. In doubtful cases the urine or the stools may be tested for lead. Every case in which lead is found in the urine is not necessarily one of lead intoxication, however, for it has been detected in a number of perfectly healthy individuals.

Blue line
wrist drop

It is impossible at present to give any general explanation for the diversity of the forms of chronic lead poisoning. The central nervous system is certainly acted on, both in its higher and lower divisions. The lead line, metallic taste and nausea, and perhaps the constipation, would seem to be connected with the excretion of the metal along the alimentary canal, while the renal action is probably of the same nature as that inducing periarteritis in the brain and, as is alleged, in the lungs under some conditions. The anæmia indicates an action on the red cells of the blood, and the gout some disturbance of the general nutrition. Attempts have been made to elucidate the nature of this action on metabolism by estimating the urea and other constituents of the urine, but no important light has been thrown on it by this means, nor in fact are significant results to be hoped for in a disease which offers so many and so diverse types as lead poisoning.

Lead acts upon so many tissues that it might be expected to have some distinctive action upon the simpler organisms, but, as a matter of fact, it seems less poisonous to them than most other heavy metals.

PREPARATIONS.

PLUMBI ACETAS (U. S. P., B. P.), lead acetate, sugar of lead ($Pb(C_2H_3O_2)_2 + 3H_2O$), forms colorless crystals, with a sweetish, astringent, afterwards metallic taste, very soluble in water, less so in alcohol. 0.05–0.3 G. (1–5 grs.).

.05-.3 g
1-5 gr

Unguentum Plumbi Acetatis (B. P.), 4 per cent.

Suppositoria Plumbi Composita (B. P.); each contains 3 grs. of lead acetate and 1 gr. of opium.

Pilula Plumbi cum Opio (B. P.) contains about 12½ per cent. of opium. 2–4 grs.

Liquor Plumbi Subacetatis (U. S. P.), *Liquor Plumbi Subacetatis Fortis* (B. P.), Goulard's extract, an aqueous solution containing about 25 per cent. of lead subacetate (approximately $Pb(C_2H_3O_2)_2PbO$). When exposed to the air, the insoluble lead carbonate is formed. The subacetate solutions are alkaline in reaction.

Only used as astringent · diarrhoea + opium in pills, burns + injection in gonorrh. Poisoning - wash, ppt with $MgSO_4$, or white of egg or milk. Remove from source give KI + good food. Opium or atropine for colic. Enema or cathartic.

Liquor Plumbi Subacetatis Dilutus (U. S. P., B. P.), lead water, Goulard's lotion or water, a solution containing about 10 parts (3 parts B. P.) of the subacetate in 1,000 parts of water.

Glycerinum Plumbi Subacetatis (B. P.).

Ceratum Plumbi Subacetatis (U. S. P.), Goulard's cerate.

Plumbi Nitras (U. S. P.) ($Pb(NO_3)_2$).

Lead plaster or diachylon plaster, *Emplastrum Plumbi*. (See Part VI.)

Therapeutic Uses.—Lead is used in therapeutics only for its astringent action. The acetate is prescribed internally in diarrhœa, generally along with opium, and always in pill form, as the solution would act on the stomach and have less effect on the bowel. It has been tried in dysentery and cholera, but has proved of little value. Lead has also been advised in cases of hæmorrhage from the lungs, kidneys and uterus, but is quite valueless here, as it acts as a styptic only when applied locally. Still less reason is there for its use in nephritis, cystitis and similar conditions.

Externally, a solution of the acetate or the dilute solution of the subacetate is used as an astringent lotion in burns and as an injection in gonorrhœa. Nitrate of lead has a reputation in the treatment of onychia.

Lead ought not to be employed externally or internally except for a short time as otherwise symptoms of poisoning may arise.

Poisoning.—In acute lead poisoning, the indications are its removal from the stomach by washing, and its precipitation, which may be best accomplished by solutions of the sulphates, such as of magnesium sulphate. In the absence of the sulphates, white of egg or milk is given to form the insoluble albuminate.

In chronic poisoning, the general treatment is the removal of the patient from the danger of further poisoning, the administration of iodide of potassium, and nutritious, strengthening diet. The iodide of potassium has been said to accelerate the elimination of lead by the kidneys, but according to Lehmann's experiments is not superior to the bromide or the chloride of potassium, and it has been recently denied that it has any effect on the excretion by the urine or by the intestine, by which most of the lead escapes from the body. In practice, however, the iodide is always used. Diuretics may be prescribed, and hot baths; sulphur baths are especially recommended, and massage is said to hasten the elimination of the poison.

In colic, morphine or opium is often necessary to allay the pain. Belladonna or atropine is used less frequently, and nitrite of amyl is said to be efficient for a short time. In the intervals between the paroxysms, a saline cathartic is often necessary to relieve the constipation, or if the vomiting prevents this, a large enema may be thrown into the bowel.

In arthralgia, the pain may necessitate the giving of opiates. In anæsthesia and encephalopathia, the treatment is expectant and symptomatic; for instance, in mania, or violent delirium, chloral may be necessary.

Paralysis treated with galvanic current. When recovery commences faradic massage.

In paralysis, strychnine may be used along with the general treatment, but the chief reliance is to be placed on the electrical stimulation of the paralyzed muscles, first with the galvanic current, and, as recovery sets in, with the induction coil. Massage of the muscles is also of benefit.

Nephritis and gout due to lead poisoning are to be treated in the same way as those arising from other causes.

In lead works and paint factories, much may be done to prevent lead poisoning. Dust is to be avoided as much as possible, and where this is necessarily present, the rooms ought to be thoroughly ventilated. The necessity of frequent bathing and of thorough washing before meals ought to be impressed on the workmen, and no food is to be admitted to the works. A lemonade made with sulphuric acid is often recommended as a prophylactic measure with the object of changing the lead to the insoluble sulphate and thus rendering it less readily absorbed. Poisoning may, however, be induced by lead sulphate, though less often than by the carbonate, which is dissolved by water in the presence of free carbonic acid, and which is changed to the slightly soluble chloride in the stomach.

When symptoms of poisoning have appeared, the patient ought not to be allowed to work again, or at least only after a long interval. Weak and anæmic men ought not to be admitted as workmen, and women are not to be employed in lead works more than can be avoided.

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Astringent - little poisonous. Metallic taste. Large quants corrosion stomach. Chronic poisoning doubtful. Only gi catarrh & nausea. Normal in tissue

V. COPPER.

Copper seldom gives rise to poisoning, and is much less frequently used in medicine than many of the other heavy metals. The soluble salts precipitate proteins from solution, and are therefore astringent when applied to the mucous membranes and to wounded surfaces. In larger quantities they are somewhat irritant and corrosive, although much less so than mercury.

Symptoms.—The copper salts have a harsh, metallic, astringent taste, and when swallowed in some quantity cause nausea, salivation and vomiting. The most of the salt is thus removed, and no further symptoms are observed. Large quantities, however, induce corrosion of the walls of the stomach and intestine, and give rise to violent vomiting and purging, the copper giving a blue or green color to the vomited matter and the stools, and blood appearing in them later from the corrosion of the mucous membrane. Violent pain in the abdomen is complained of, and the usual symptoms of acute corrosive poisoning may follow—collapse, with weak pulse and respiration, headache, giddiness, unconsciousness, delirium, coma, convulsions and paralysis. These may prove fatal in a few hours, but more frequently the patient lives for several days to sink eventually from exhaustion.

The nausea, vomiting and purging of acute copper poisoning are due to the local effect on the mucous membranes of the stomach and intestine. In fact, although some copper is absorbed in these cases, there is no reason to suppose that any of the acute symptoms are due to it, for they are all induced by other poisons which act only as gastro-intestinal irritants.

It is still disputed whether **chronic copper poisoning** occurs in man. The question is of great hygienic interest, because copper is used very often to give color to preserved vegetables, such as peas, is added to flour to improve the bread, and may enter into the food from the use of copper cooking vessels and in a variety of other ways. In copper and brass workers, gastro-intestinal catarrh, or colic and diarrhœa, occur occasionally and are ascribed to the copper swallowed in the course of their occupation. The dust inhaled may similarly cause laryngeal irritation and bronchitis. The skin and hair have often a greenish tint, and a green line on the teeth, just where they enter the gums, is known as the copper line; but it is believed that these are due largely to the copper dust deposited on the skin, hair and teeth, and not to the excretion of the metal. Local paralysis, anæmia, tremor, emaciation and cutaneous eruptions are said to have followed these symptoms in some cases, and have been held to indicate that copper is poisonous after absorption, but it may fairly be doubted whether these symptoms are really due to the copper or to the lead, arsenic and other poisons often associated with it. It is certain that only a very small proportion of workers suffer from any symptoms whatever, and that the great majority enjoy excellent health. Furthermore, copper has been taken in the form of the metal, or of its soluble salts for prolonged periods without any symptoms being elicited except those of slight intestinal catarrh and some nausea. Animals have been fed with food containing large doses of copper for many months, apparently without any symptoms of poisoning, and copper is found so regularly in the tissues of man and animals that it may be regarded as a normal constituent, although its function is altogether unknown and it may be merely stored up on its way to excretion. Of course it is possible that there exists in certain persons an idiosyncrasy for copper, and that these suffer from the ingestion of quantities

Frogs - action on heart & cns = heart paralysis. Emesis from direct action on stomach. Absorbed by mm. (of g.i.) & raw surfaces. Lodged in liver; also kidney, spleen, thyr
By mouth not poisonous as slowly absorbed & bound down by liver.

which are harmless in others. But until the symptoms have been more definitely determined, and have been shown not to arise from the other poisons associated with copper, it is impossible to consider this form of intoxication as satisfactorily established, and there is no reason to suppose that poisoning can be induced by small quantities of copper such as are contained in preserved vegetables or in food cooked in copper vessels.

In animals the general action may be elicited by the injection of copper into the blood or subcutaneously. The ordinary salts are inadmissible by the former method, as they precipitate the proteins of the blood and cause embolism, and double salts, such as the tartrate of copper and sodium, have therefore been used. In the frog copper induces great weakness and eventually complete paralysis of the spontaneous movements and of the heart. Harnack attributed this to direct action on the muscle, but later observers have found that the central nervous system is primarily affected, and that the muscles retain their irritability after complete paralysis of the spinal cord. There is, however, a direct action on the muscles also, for they lose their irritability very soon after death and even before the spontaneous movements have ceased the contraction of the muscles on direct stimulation is much weaker than usual. Very often fibrillary contractions are observed early in the frog, but it is unknown whether these are of central or of peripheral origin. The heart is somewhat accelerated at first by very small quantities, but later becomes slow and weak, and finally ceases in diastole before the skeletal muscles are paralyzed; the changes in the heart are due to direct action on the muscle.

In mammals the intravenous injection of copper does not cause vomiting according to most authors, thus proving that the emetic action is due to the irritation of the stomach, and not to any action on the medulla. When large quantities are injected, the locomotion soon becomes slow, clumsy and weaker, and later complete paralysis of the spontaneous movements follows. The heart and respiration seem equally involved, but the respiration ceases somewhat earlier than the heart. The blood-pressure rises slightly after the intravenous injection of copper, but afterwards falls, partly on account of the weakness of the heart, and partly from failure of the vasomotor nerves to maintain the contraction of the blood vessels. When an animal survives longer, violent, sometimes bloody, diarrhœa is generally induced by copper, as by most of the other heavy metals. The animals lose flesh rapidly, and refuse food, and the urine often contains albumin, and according to some authors, hæmoglobin and blood. In the rabbit some icterus and anæmia is said to occur from the destruction of the red blood cells, and fatty degeneration of the liver, kidney and heart has been observed. Others have found ecchymoses and congestion along the intestine and in the kidney to be the chief lesions. Similar results are obtained in rabbits when copper is given by the mouth, as this animal is incapable of rejecting the poison by vomiting. In the dog, on the other hand, poisonous doses are removed by vomiting when they are given by the mouth.

Copper is certainly absorbed from the stomach and intestine, for large quantities have been found in animals fed on it for some time. Baum and Seeliger state that a very large proportion of the poison is absorbed when small doses are given, but the proportion lessens as the dose is increased. It also passes into the blood from other mucous surfaces and from wounds. It is said to have a strong affinity for hæmoglobin and to form with it a compound which Kobert has named cuprohæmol, and which is stated to be formed very rapidly when copper is injected into the blood, the metal leaving the serum and attaching itself to the corpuscles at once. The copper absorbed from

Excreted GI. urine bile saliva. Very destructive to some algae. Favors grape vine growth. 1% stops bact. growth. As emetic .1-.3 G CuSO4 - 1% Deposit about P particles + emesis ? P antidote. 1% ext — gonorrhea, ulcers, astringent escharotic

the intestine and stomach is lodged chiefly in the liver, less in the spleen, kidney and thyroid. It is excreted in the bile, urine and saliva, in the intestinal secretions, and ~~in~~ traces in the milk, and is said to pass from the mother to the fœtus in utero. Copper is found in small quantities in these organs and secretions in man and in animals that have not been treated with it, but in much larger amount after prolonged administration. Taken by the mouth, it fails to cause general poisoning, because it is slowly absorbed, and also because what is absorbed is withdrawn from the blood by the liver.

Copper is found as a normal constituent of the blood in many of the invertebrates, in which it performs the same function as the iron of the hæmoglobin in the vertebrates. It has been detected in one of the pigments of birds' feathers, and, as has been stated, is so frequently found in the tissues of mammals, both wild and domesticated, that it may be regarded as a normal constituent. Oysters and other animals take it up in large quantities when they live in water rich in copper, and apparently are not injured by it. Many of the higher plants, notably the grape vine, are said to be remarkably improved by the sprinkling of copper on their leaves, and this is not only from the destruction of parasites, for vines free from any disease show a more luxuriant foliage and bear more and larger fruit than other healthy plants, which are not treated with it. On the other hand, copper is a deadly poison to several of the lower plants. Thus traces of copper added to the water in which they live, destroy some of the simpler algæ, and Naegeli asserts that one part of copper in one thousand million parts of water is sufficient to kill these plants. The parasites of the grape vine, potato, apple and other plants are destroyed by spraying the plants with copper, and yeast ceases growing in a 0.02 per cent. solution, while the moulds seem to be almost immune to its action. Locke found that the traces of copper contained in water distilled in copper vessels was sufficient to destroy tubifex (one of the annelid worms) and tadpoles, while Bucholtz states that the development of bacteria is stopped by a solution of copper sulphate under one per cent. in strength. Copper thus seems to have a very powerful poisonous action on certain living forms and to be harmless to others, and the subject deserves further investigation. It is possible that it may prove to act prejudicially to some human parasites, and it is certainly less dangerous to man than many other remedies used as parasiticides and disinfectants.

PREPARATIONS.

As emetic .3-.6 G

Cupri Sulphas (U. S. P., B. P.) ($CuSO_4 + 5H_2O$), large, transparent, deep blue crystals, without odor, but with a nauseous, metallic taste, soluble in water, scarcely so in alcohol. Dose as an emetic, 0.3–0.6 G. (5–10 grs.).

Therapeutic Uses.—Copper sulphate is used internally only as an emetic, and for this purpose ought to be given in about one per cent. solution. It acts promptly, and does not leave so much depression and nausea as other metallic emetics, and for this reason is unsuitable as an expectorant. In phosphorus poisoning it is especially valuable, as in addition to causing evacuation of the stomach, the metal is deposited on the particles of phosphorus and prevents their absorption.

Externally copper sulphate is used as an astringent injection in gonorrhœa, and occasionally as a lotion in ulcers and wounds; for this purpose it is employed in 1 per cent. solution. The solid crystals are

+ putrefactive algae in sewage + water (drinking) used - high dilutions)
Milk, egg, Ta, magnesia to form non-corrosive comps in poisoning.
Zinc. like Cu = astringent - insol alb. Large doses = irritants + corrosive
Sulphate less irritant than chloride, latter for caustic + disinfection action.
Small dose Zn = nausea, vomiting [illegible] vomit. Large = no vomit - collapse

sometimes used to touch exuberant granulations for their astringent and corrosive effect.

Small quantities of copper sulphate have recently been used to destroy the algæ which grow in reservoirs and often give the water a disagreeable odor and taste. The proportion of copper required for this purpose is about one part in a million or sometimes in fifty millions; this treatment does not render the water deleterious to man, for much larger quantities of copper have been taken constantly without injury. It has also been suggested to disinfect water contaminated with typhoid bacilli, and some success has been recorded, though these organisms are less susceptible to copper than those of putrefaction; the proportion of copper required for this purpose appears to be greater than that necessary to destroy the less resistant algæ.

The chloride of copper is a much more irritant and disinfectant substance than the sulphate.

In cases of **Poisoning** with copper salts, the stomach generally rejects the metal by vomiting and no emetic is required. Non-corrosive compounds may be formed by giving milk, egg, or other forms of albumin, tannic acid, magnesia, or ferrocyanide of potassium. Morphine may be required for the pain, ice to stop the vomiting.

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VI. ZINC.

The effects of zinc resemble those of copper so closely that they need only brief mention. Like copper, the soluble salts form insoluble albuminates and therefore possess an astringent action, or in large quantities act as irritants and corrosives. The sulphate is the soluble salt most commonly used in medicine, but the chloride has frequently given rise to corrosive poisoning, and is therefore of greater importance than the chloride of copper. The sulphate is much less irritant and more astringent than the chloride, which is used only as a caustic and disinfectant.

Symptoms.—The sulphate of zinc has a harsh, metallic taste, and in small doses causes nausea and vomiting, in larger quantities violent

Continued [illegible] digestion [illegible] in fumes = brassfounders ague (see below). General action only when double salts by hypo - depresses cns, heart [illegible] liver etc. Excreted g.i. bile + urine. / and vol. muscles [illegible] congestion of g.i. mm + kidney. General weaker than in [illegible]

vomiting and purging, pain in the abdomen and collapse; these symptoms are due to the local action on the stomach and intestine. The insoluble zinc oxide and carbonate are less liable to cause acute irritation than the sulphate, but their prolonged ingestion has given rise to dyspepsia and constipation or diarrhœa in some cases. The continued administration of zinc salts has no effects in man, except those of disordered digestion and constipation, and Lehmann could detect no effects in the dog after the administration of 155 G. of the carbonate in the course of 335 days, although a considerable amount of the metal had been absorbed.

In workers in zinc, a curious condition known as brassfounders' ague is occasionally met with. It is ushered in by a sense of general discomfort and weakness, with more or less pain in different parts of the body; later ~~prolonged rigors~~ and shivering are followed by a rapid acceleration of the pulse, coughing and soreness of the chest and headache. These symptoms give place to profuse perspiration, and the patient sinks into a sleep from which he awakes in ordinary health. The attacks may return frequently, and seem to be due to the fumes of zinc which escape in the process of casting. A number of obscure nervous conditions have also been described as arising from zinc in workmen in brass factories and bronze works, but they seem to be extremely rare, and it is questionable whether they are really due to the zinc or to its impurities, such as arsenic and lead.

Action.—The general action of zinc can therefore be observed only when it is injected intravenously or hypodermically. For this purpose, the double salts alone can be used, as the ordinary ~~salts~~ precipitate the proteins of the blood when injected into a vein, and cause acute irritation when applied subcutaneously. In the frog, zinc is found to cause weakness and lessened reflex excitability and the heart becomes weak and inefficient, irregular and slow, and eventually ceases in diastole. The action seems to be exercised chiefly on the central nervous system and the heart, although the voluntary muscles respond more weakly to the electric current in life and lose their irritability entirely soon after death.

In mammals, the intravenous injection of zinc causes vomiting and diarrhœa, weakness, tremor and paralysis of the extremities; and the stomach, intestine and heart contain small hæmorrhages. The blood-pressure seems to be but little affected, until just before death, but the pulse is slowed. Helpup found that the subcutaneous injection of zinc salts induced congestion and parenchymatous inflammation of the kidney.

Zinc seems therefore to depress the central nervous system and to a less extent the heart and voluntary muscles, and to cause irritation and congestion of ~~the~~ mucous membrane of the stomach and ~~intestine and inflammation~~ of the kidney. ~~The fact that~~ vomiting occurs from the intravenous injection of zinc ~~salts~~ might seem to indicate that it acts directly on the medullary centre for vomiting, but may more probably be explained by the metal inducing inflammation in the stomach.

Lehmann found that of the zinc absorbed from the stomach and intestine, most is contained in the liver and bile, less in the spleen, kidney, thyroid and pancreas, and very little in the other tissues. Zinc is excreted by the stomach and intestinal walls and in much smaller amounts in the bile and urine.

Locke found zinc to possess a poisonous action on the tadpole and tubifex when present in traces in the water in which they lived, but this effect was

Unguentum zinci oxidi 20% NB. as brain sedative.
Ext sulph in sol, or oxide or carbonate as powders + ointment as astringents
(eye wash 1/2% + gonorrhoea 4% → skin diseases.

$ZnCl_2$ a powerful caustic

Poisoning treated as was copper

weaker than that of copper. Richter states that zinc is less poisonous to fungi than copper, and very weak solutions seem to promote their growth. The zinc salts seem to be in general much weaker than those of copper, which they resemble closely in other respects.

PREPARATIONS.

ZINCI SULPHAS (U. S. P., B. P.) ($ZnSO_4 + 7H_2O$), colorless, transparent, odorless crystals, with a harsh, astringent, metallic taste, soluble in water, not in alcohol. 0.5–2 G. (8–30 grs.), as emetic; 0.05–0.2 G. (1–3 grs.), in epilepsy. Emetic .5-2 G

Zinci Oxidum (U. S. P., B. P.) (ZnO), an amorphous white powder without odor or taste, insoluble in water. 0.1–0.5 G. (2–8 grs.).

Zinci Carbonas Præcipitatus (U. S. P.), *Zinci Carbonas* (B. P.), a preparation varying somewhat in composition, but always containing some oxide, which it resembles in appearance and solubility. 0.1–0.5 G. (2–8 grs.).

UNGUENTUM ZINCI OXIDI (U. S. P.), 20 per cent. ZnO 20%

UNGUENTUM ZINCI (B. P.), 15 per cent. of the oxide.

Zinci Stearas (U. S. P.).

Unguentum Zinci Stearatis (U. S. P.), 50 per cent.

Unguentum Zinci Oleatis (B. P.).

Zinci Chloridum (U. S. P., B. P.) ($ZnCl_2$), a white powder, or porcelain-like mass, irregular or moulded into pencils, odorless and strongly caustic, very deliquescent and soluble in water and alcohol.

Liquor Zinci Chloridi (U. S. P., B. P.), 50 per cent. U. S. P., 75 per cent. B. P.

Zinci Sulphocarbolas (B. P.), *Zinci Phenolsulphonas* (U. S. P.) ($Zn(C_6H_5SO_4)_2 + 8H_2O$), colorless crystals with an astringent taste, soluble in water and in alcohol. Used externally in 1 per cent. solution. (See page 473.)

Therapeutic Uses.—Zinc sulphate has been used internally as an emetic, but not so widely as the sulphate of copper, although it is equally efficient. The sulphate, the oxide and the carbonate have been advised in the treatment of various brain diseases, from the erroneous belief that zinc is a sedative. The oxide and sulphate are seldom employed as astringents in diarrhœa.

Externally the zinc preparations, with the exception of the chloride, are used as astringents, the sulphate being applied in solution, the oxide and carbonate as powders or as ointments, which most prefer to the oleate. The oxide is especially useful as an application in many skin diseases. Solutions of the sulphate are used as an eye wash (one-half per cent.) and as an injection in gonorrhœa (1–4 per cent.). In the last case it is sometimes formed into a mixture with acetate of lead, the sulphate of lead which results being credited with some astringent action and not being washed off so readily from the diseased surface. The sulpho-carbolate is also used as a urethral injection, and the salicylate and the sulpho-iodolate of zinc have also been introduced as astringent and antiseptic applications.

The chloride of zinc differs from the other salts in being a powerful caustic, and is used as a paste or in pencil form to destroy malignant growths, or in chancres and gangrenous sores. It produces a white eschar and is said to be less liable to spread over the surface than potash, but penetrates the epidermis

AgNO$_3$ = caustic, astringent & disinfectant. White alb → black, sol in chlorides
Dil astringent or irrit, then strong caustic. Vessels not contracted
If swallowed usual G.I. sym – C.N.S. sym. P.M. shows usual corrosion.

with difficulty, and it is therefore advisable to destroy this with potash or a blister before applying the caustic. It is sometimes mixed with flour or dried gypsum and water to a paste (Canquoin's paste), when a less active caustic is desired. Its use is much more restricted at the present time than formerly. Burnett's disinfecting solution (a somewhat stronger solution than the official liquor) is used to disinfect fæces and urinals and the liquor of the pharmacopœia may be employed for the same purpose. It has frequently given rise to severe corrosive poisoning from being swallowed accidentally or suicidally.

The acetate, bromide, iodide and valerianate have exactly the same effect as the sulphate and are quite superfluous. Poisoning with zinc is treated in the same way as that with copper.

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VII. SILVER.

The only salt of silver used at all extensively in medicine is the nitrate, which is caustic, astringent and disinfectant. Added to solutions of proteins, it forms a heavy precipitate of albuminate, which is at first white in color, but turns darker in the light as the silver is reduced, and which is soluble in the presence of chlorides.

Symptoms.—In dilute solution silver is a slight irritant to the skin, and causes redness and itching only, but more concentrated solutions blister, and the solid nitrate of silver causes an eschar, which is at first white, but later turns black from the reduction of the silver in light. On the mucous membranes, dilute solutions act as astringents, but concentrated cause irritation and corrosion. The caustic action of silver does not extend so deeply as that of some other metals, such as mercury, because the penetration of the metal is limited by the membrane of silver albuminate formed. On the other hand, the silver salts are more irritant than those of lead.

The astringent action is to be attributed not to any action on the vessels, but to the formation of a protective layer of coagulated albumin. If irritation is induced the vessels are dilated, and there is no evidence that they are ever contracted in the practical use of silver.

In acute silver poisoning from the ingestion of silver nitrate, the symptoms are those of severe gastro-intestinal irritation and corrosion. Burning pain is felt in the throat and stomach, and is followed by nausea and vomiting and often by purging. The mouth is covered with a grayish-white membrane, which turns darker after a time, but this is absent if the poison be swallowed in the solid form, as has happened sometimes. The corrosion of the stomach and intestine causes collapse, with weak pulse, shallow respiration and pinched features and

General action (experimentally injection of non ppt. salt) – Action on medulla also CNS. Excretion acts on gums. Kidney irritation & oedema of lungs. By mouth very little absorbed. In leucocytes & cells as organic pigment & left (dark skin [illegible]) Argyria slate-greyline

this may be followed by coma, convulsions and death. The throat, stomach and intestine presented the ordinary appearances of acute corrosive poisoning in one case in which an autopsy was performed.

Action.—The symptoms of acute poisoning are due to the local action, and present no features suggesting that silver is absorbed and causes general poisoning. The action of silver after absorption has, however, been investigated in animals poisoned by subcutaneous or intravenous injection. The nitrate, owing to its coagulating properties, is unsuitable for this purpose, and the hyposulphite of sodium and silver, or a solution of the albuminate has therefore been used. In mammals the central nervous system is the chief seat of action, especially the medulla oblongata, which seems to be stimulated at first, for the blood-pressure rises and the pulse is somewhat slow, owing to increased activity of the vasomotor and vagus centres. Later the blood-pressure falls and the respiration becomes slow and labored, and eventually ceases from paralysis of the centre. Gaethgens asserts that the diaphragm, and eventually the other striated muscles are paralyzed soon afterwards. The heart is comparatively little affected and often continues to beat some time after the respiration has stopped. In less acute poisoning, when the animal survives the injection for several hours or days, a marked increase in the bronchial secretion, culminating in œdema of the lungs, has been noted; no satisfactory explanation of this has been advanced, but it does not seem due to cardiac inefficiency and occurs also when the excised lung is perfused with blood containing silver. Congestion and ecchymoses are found in the stomach and intestine, and some authors mention ulceration of these mucous membranes. Cohnstein found that small quantities of silver salts injected intravenously cause some increase in the urine for a time, but that larger quantities are followed by albuminuria.

In cold-blooded animals and in invertebrates, silver preparations are said to cause violent convulsions, resembling those of strychnine and followed by general paralysis.

The general action of silver is thus apparently directed first of all against the medulla oblongata, the rest of the central nervous system being affected to a less extent. The mucous membrane of the stomach and intestine is acted on, as by most heavy metals, and the kidney is also liable to irritation. Œdema of the lungs occurs frequently.

Chronic Poisoning.—There is no evidence that in acute poisoning in man any considerable amount of the metal is absorbed from the stomach and intestine. When silver is given for prolonged periods, however, some is absorbed, although probably only a minute fraction of that actually swallowed. In the stomach small quantities of soluble silver salts are probably changed to the chloride and albuminate, but the form in which the metal is absorbed has proved a subject of dispute. It seems to be taken up in solution, for none of it is found in the epithelium of the stomach and intestine, and some of it may circulate in the blood in a soluble form for a short time. But the greater proportion is very soon thrown down in the form of minute granules, which were formerly believed to be metallic silver, but which have more recently been said to be one of its organic compounds. The formation of this pigment is quite different from the reduction of silver in sunlight, for it occurs in complete darkness. The change apparently takes place in the cells, especially in the leucocytes, but the granules are afterwards extruded into the surrounding fluid.

Pigment. only Argyr. [illegible]

They are found in the connective tissues of the body chiefly, and when present in quantity, give a dark color to the skin and mucous membranes. This pigmentation (Argyria) was much commoner formerly than at the present time, but several cases have been described quite recently. The chief source of chronic silver poisoning or argyria was formerly the treatment of epilepsy with the nitrate. More recently it has occurred in the makers of artificial pearls, who use silver as a pigment.

Local argyria is sometimes met with from the prolonged application of silver nitrate to the eye or throat, when it tints the eyelids and mouth, and from working with silver, when the hands are permanently blackened from the granules being forced into the skin.

The deposit of the silver in the skin gives it a darker color, varying from light gray in mild cases to a darker slate shade after more prolonged use. It is generally distributed all over the body, but in some cases has been especially marked in the face, and it is said to begin in the gums, where it causes a dark, slate-colored line somewhat resembling the lead line. In the skin it is found in the corium, not in the epidermis. The deposit and the dark color extend throughout the alimentary canal and the respiratory passages, the granules occurring in the connective tissue, particularly in the intestinal villi, and not in the epithelium. The glomeruli of the kidneys, the connective tissue of the liver and spleen, the choroid plexus, the tunica intima of the aorta, the serous membranes, and the mesenteric lymph glands contain more of the deposit than other organs. The pigmentation is not accompanied by any other symptoms of importance, and the victims live to old age without suffering from the chronic poisoning in any way, except from the annoyance induced by the change in color.

Argyria is quite incurable, although many attempts have been made to remove it. Iodide has been tried, for the most part without effect, and blistering is equally valueless, as the pigment lies deeper than the epidermis. The only known solvent of the granules is cyanide of potassium, and of course this is inadmissible, owing to its powerful poisonous action.

Argyria has been induced in animals by prolonged treatment with small doses of silver salts, though the pigment is not found in the skin in them, but in the duodenal mucous membrane and the mesentery attached to it, the mesenteric lymph glands, the spleen and liver. A still more limited area of argyria has been caused in animals recently by administering for a few weeks the glycyrrhizinate of silver. It is not unlikely that more prolonged administration would lead to other organs, and perhaps the skin, being involved. A deposit of silver pigment has also been induced in animals by a single injection of a non-irritant preparation into a vein, or into the subcutaneous tissue. Here the silver is found at first in the liver capillaries, the glomeruli of the kidney, the intestine and the bone marrow, but is afterwards taken up by the leucocytes, and carried to all the organs of the body.

What is absorbed is fixed in tissue & not eliminated. A powerful antiseptic. Reduced by organic substances & light.
U.S. in C.N.S. diseases as epilepsy. Ext lunar caustic for warts, cap hemorrhage & to destroy false membranes

In man it seems likely that most of the silver passes through the alimentary canal unabsorbed and that the small proportion taken up by the tissues is precipitated and remains embedded in them indefinitely, for the pigmentation remains unchanging in its depth, and there is therefore no reason to suppose that any of the silver is eliminated.

In animals, however, some of the silver injected hypodermically or intravenously is excreted by the epithelium of the alimentary canal. None appears in the urine. In the frog silver injected hypodermically is all excreted by the epithelium of the tongue, is swallowed, and passes out in the fæces. No other poison is known to be eliminated by this channel.

Silver nitrate is a powerful antiseptic, partly from its action in coagulating the proteins of the microörganisms, partly from the specific effects of the metal, as is shown by the fact that the albuminate of silver is also an active disinfectant.

Argenti Nitras (U. S. P., B. P.) ($AgNO_3$), colorless crystals which become gray or grayish-black on exposure to light in the presence of organic matter, with a bitter, caustic, strongly metallic taste, very soluble in water, less so in alcohol. 0.01–0.03 G. ($\frac{1}{6}$–$\frac{1}{2}$ gr.) in pills made up with kaolin.

.01-.03 G

ARGENTI NITRAS FUSUS (U. S. P.), moulded nitrate of silver, lunar caustic —a white, hard solid, generally cast in the form of pencils.

lunar caustic

ARGENTI NITRAS INDURATUS (B. P.), toughened caustic, a silver nitrate fused with 5 per cent. of nitrate of potassium.

Argenti Nitras Mitigatus (B. P., U. S. P.), mitigated caustic, consists of one part of nitrate of silver and two parts of nitrate of potassium fused into rods like lunar caustic.

The silver preparations ought to be kept in dark amber-colored bottles, in order to prevent their being reduced by light, and ought not to be prescribed with organic matter, which rapidly reduces them.

Therapeutic Uses.—Silver nitrate pills have been recommended in some forms of dyspepsia and vomiting, and in gastric ulcer, and have also been used as astringents in diarrhœa, but generally with little benefit. A very ancient use of silver oxide and more recently of the nitrate, is that in the treatment of epilepsy, chorea, tabes and various other nervous diseases. This dates from the Arabs, and is said to have originated from the astrological medicine of that period, which taught that nervous diseases were especially affected by the phases of the moon, which was associated with silver in their system (hence, lunar caustic, lunacy). Clinical experience shows that silver is of no benefit in epilepsy, and, in fact, it is improbable that silver reaches the central nervous system in any other form than inert granules. This use of silver very often gave rise to argyria without benefiting the patient, about 15–30 G. proving sufficient to cause marked pigmentation.

Externally silver nitrate is employed very extensively, the sticks of lunar caustic being used to destroy warts and other small skin growths, to arrest capillary hæmorrhage, to destroy the false membranes of diphtheria and for other similar purposes. Where a milder caustic

mitigated — some now pref. to wash new born infants' eyes.
$AgNO_3$ 1:500 – 2500 – gonorrhea. 15–30 G in a few months will produce argyria. If poisoning – salt sol., eggs, milk.

1/250

is required the mitigated caustic is used instead of ordinary lunar caustic. A solution of 2–5 per cent. may also be applied to cauterize chancres and indolent ulcers, and one of 1–2 per cent. may be painted on mucous membranes as an irritant disinfectant. A solution of common salt is then used to wash the part, in order to remove the excess of silver. In ophthalmia, especially of the infectious form, a solution of 1–2 per cent. is extremely valuable, and, in fact, a routine treatment in some lying-in hospitals is to wash the eyes of the infant with this solution immediately after birth as a prophylactic measure to prevent ophthalmia. A solution of this strength is only to be used by the surgeon himself, and the eye should be washed out with a salt solution at once. A more dilute solution (one fourth to one half per cent.) may be used as a lotion for the eye more frequently, may be applied to extensive denuded surfaces, as burns, and is often thrown into the rectum in chronic dysentery. In gonorrhœa, the nitrate of silver, 1 part in 500–2,000 of water, is used as an injection, and is found to have great value, destroying the gonococci and promoting healing. Very much stronger solutions (up to 5 per cent.) have been used to abort the disease in its onset, but cause great pain.

PREPARATIONS.

The precipitation of silver nitrate by proteins and chlorides confines its disinfectant action to narrower limits than those of some other bactericides, and this has led to the introduction of a number of other compounds, which are less easily dissociated and accordingly less liable to be thrown out of solution. Thus *argentamine,* a 10 per cent. solution of silver phosphate in 10 per cent. ethylendiamine solution, has been used, in gonorrhœa diluted to 1:1,000–5,000, in the eye in 5 per cent. solution. It penetrates better than silver nitrate, but the alkaline diamine renders it somewhat irritating. Another recent product is *argonin,* which is a combination of casein and silver, is soluble in water, and, like argentamine, is not precipitated by chlorides nor by albumin; it is a somewhat weaker disinfectant than the nitrate and argentamine. The lactate of silver, *actol,* and the citrate, *itrol,* have also been used as disinfectants. Actol is soluble in water and resembles the nitrate in coagulating proteids, while itrol, on the other hand, is practically insoluble (1 to 3,800 water). The former is used in solution (½ per cent.), the latter as a disinfecting powder in wounds. Actol and argonin have been shown to have very considerable disinfectant power in test-tube cultures, and actol lessens the putrefaction in the bowel and constipates to some extent, but argonin has no effect on the intestinal microbes. *Protargol, largin, argyrol* and many other compounds of silver have been introduced, but the best known in the last few years has been Credé's *colloid silver* (*Collargol*), which is metallic silver in colloid form, which may be suspended in water (4 per cent.) or in ointment (10–15 per cent.). This has been advertised as a bactericide in the most diverse conditions, and has been injected hypodermically, and even intravenously, to destroy microbes in the tissues. But it has no disinfectant action, and in fact is a very inert body, which is devoid of any therapeutic properties. It may be added that none of these newer preparations are superior to the nitrate in efficiency as disinfectants, and those that are less irritant are also less reliable.

Silver preparations ought not to be used for long periods, as argyria has been induced in three months and after the use of 15–30 G. (½–1 oz.) of the nitrate.

G.I. Tr. irritation & for granulating wounds - Black stools - Very little absorbed. Rarely poisoning, unless in X ray work nitrites from nitrates. & formation of methaemoglobin

In cases of poisoning with silver nitrate, eggs, milk and, above all, common salt solution are indicated to form insoluble compounds. In argyria no improvement can be expected, though the iodide of potassium may be tried.

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VIII. BISMUTH.

The insoluble salts of bismuth, in especial the subnitrate, have long enjoyed a reputation in the treatment of gastric and intestinal irritation, and have more recently been advised in surgery as applications to granulating wounds.

Symptoms.—Taken in therapeutic doses, the subnitrate induces no marked symptoms, even after prolonged use. It has little or no taste, and passes through the stomach and intestine for the most part unabsorbed. It is said to increase the peristalsis of the stomach and the secretion of mucus, but it may be questioned whether it has more effect here than any other heavy powder. In the intestine it is said to have some effect in increasing the leucocytes of the blood, and often causes some constipation. It gives the stools a black color, which is generally believed to be due to the formation of the sulphide of bismuth, but which Quincke ascribes to the reduction of the subnitrate in the intestine.

Very little of the bismuth swallowed is absorbed, but several authorities have found traces in the urine of patients treated with it internally, so that some evidently passes into the blood under certain unknown conditions. Enormous quantities have been administered internally without any symptoms of poisoning being elicited, but in one or two cases some stomatitis has been remarked, while in other instances large concretions of bismuth have been found in the stomach and bowel.[1] Some of the older writers describe serious poisoning from bismuth, but this was not due to the drug itself, but to the lead, arsenic, or antimony with which it was contaminated.[2] Since its use

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[1] Large quantities of bismuth subnitrate have been given by the mouth or rectum in Röntgen-ray examination of the stomach and bowel, and in a few cases fatal poisoning has occurred from nitrites being formed from the nitrate and leading to the formation of methæmoglobin in the blood cells.

[2] A symptom formerly noted in cases treated with bismuth was an extremely disagreeable odor in the breath, but this has been shown to be due to the presence of tellurium in the preparation.

'In raw surfaces = Sx. sym, salivation, pain, swollen gums, albuminuria.
Off. when dressing off

was extended to wounded surfaces, several cases of serious intoxication have occurred. The symptoms are salivation, swelling of the gums, tongue and throat, pain and difficulty in swallowing, black spots in the mouth and throat, and gangrene of the soft palate and other parts of the mucous membrane of the mouth. Vomiting, diarrhœa and albuminuria follow, but the patients generally recover when the dressing is removed from the wound. In these cases much less bismuth is applied than is often prescribed for internal use, so that it would appear that it is absorbed more rapidly from granulating surfaces than from the mucous membranes, or that what is absorbed from the stomach and intestine is prevented by the liver from reaching the general circulation.

Action.—The general action of bismuth has been studied in animals by the subcutaneous or intravenous injection of the double salts, such as the tartrate of bismuth and sodium. In frogs the symptoms are those of stimulation of the spinal cord and medulla oblongata, followed by depression and paralysis. The stimulation induces tonic convulsions, which are separated by periods in which the frog is at first apparently normal, but in which symptoms of depression and paralysis appear later. The peripheral nerves and muscles and the heart are little affected.

In mammals also large doses act chiefly on the central nervous system. The respiration is accelerated, the heart slowed and violent clonic and tonic convulsions follow at short intervals, during which the movements are weak and incoördinated. Toward the fatal issue of the injection the heart often ceases entirely for some time and then regains its former rhythm quite suddenly. The blood-pressure falls, partly owing to the weakness of the heart, partly from depression of the vasomotor centre. In some animals the respiration ceases before the heart; in others the sequence is reversed. The heart seems to be affected directly, for division or paralysis of the vagus nerves does not alter the effects.

Smaller quantities injected intravenously or subcutaneously into mammals induce a more chronic form of intoxication, which resembles that seen in man. The earliest symptoms are loss of appetite, vomiting and diarrhœa, salivation and stomatitis with ulceration of the gums, tongue and buccal mucous membrane. Weakness, slowness and incoördination of the movements follow, and except in very few chronic cases, tetanic convulsions occur at intervals. The urine contains albumin and casts. The weakness gradually deepens into complete paralysis and the animal dies, generally without convulsions. The heart seems little affected in the chronic intoxication, but the blood-pressure is low from the intestinal irritation and general collapse.

Besides the stomatitis and ulceration of the mouth, the post-mortem appearances in chronic bismuth poisoning in animals consist in some congestion, inflammation and necrosis in the kidney, and an intense black coloration of the cæcum and the upper part of the large intestine. This pigmentation is limited very exactly by the ileocæcal valve, and extends throughout the thickness of the bowel wall. The mucous membrane may also be necrosed in places and ulcers and hæmorrhages are met with in it. The black coloration is due to a deposit of bismuth sulphide on the mucous membrane and in the capillary vessels and lymph spaces. Meyer and Steinfeld found that bismuth is excreted all along the alimentary canal, but in larger quantities in the cæcum and large intestine than elsewhere, and they ascribe the ulceration to the precipitation of the sulphide in the vessels and the consequent arrest of the blood current. When sulphide solution was artificially introduced into the stomach and small intestine, bismuth caused necrosis and ulceration here also, so that there is considerable support for this view.

See animal exper. — ~~all~~ 2nd par.
Protective & astringent in G.I. catarrh & ulcer — protects whole stomach from food & juice
Ditto for diarrhoea. Absorbtive powder in surgery — but poison.
Bi for its insolubility (X-ray etc)

They found bismuth to be stored in considerable quantity in the liver and to be excreted by the urine, stomach and intestine, but especially by the cæcum and large bowel. It has been found in the saliva by other observers, and perhaps in traces in the milk, although the last is not satisfactorily established.

The action of bismuth in acute poisoning in animal experiments seems therefore to be exerted on the medulla and spinal cord, to a less extent on the heart, while in chronic intoxication the organs affected are those by which it is excreted—the mouth, kidney, large intestine and cæcum.

PREPARATIONS.

BISMUTHI SUBNITRAS (U. S. P., B. P.), white bismuth, Magisterium Bismuthi, bismuth oxynitrate, a heavy white powder, odorless and almost tasteless, insoluble in water or alcohol but soluble in nitric or hydrochloric acid. It consists of a mixture of the hydrate and subnitrate of bismuth in varying proportions. 0.3–2 G. (5–30 grs.), in powder or suspended in water. 0.3-2G

✓ *Bismuthi Subcarbonas* (U. S. P.), *Bismuthi Carbonas* (B. P.), bismuth oxycarbonate, a white or pale yellowish-white powder, varying in composition, odorless, tastless, insoluble in water or alcohol. 0.3–2 G. (5–30 grs.) in powder.

Trochiscus Bismuthi Compositus (B. P.); each contains 2 grs. of bismuth oxycarbonate along with the carbonates of magnesia and of lime.

Bismuthi Salicylas (B. P.), *Bismuthi Subsalicylas* (U. S. P.) the salicylate or oxysalicylate of bismuth, is a white, amorphous powder, insoluble in water. 0.25 G. (4 grs.).

Bismuthi Citras (U. S. P.) ($BiC_6H_5O_7$), a white powder, odorless, tasteless, insoluble in water or alcohol, used only to form

Bismuthi et Ammonii Citras (U. S. P.), small, shining, translucent scales, odorless, but with a slightly acidulous and metallic taste, and becoming opaque on exposure to the air, very soluble in water, less so in alcohol. 0.12 G. (2 grs.).

✓ *Liquor Bismuthi et Ammonii Citratis* (B. P.) contains the equivalent of 5 per cent. of bismuth oxide. ½–1 fl. dr.

Bismuthi Subgallas (U. S. P.), 0.25 G. (4 grs.), forms a white or nearly white powder, insoluble in water, tasteless and odorless. ʒ

Therapeutic Uses.—Bismuth has been used chiefly in gastric catarrh and ulcer, and has often been looked upon as a specific in the last affection, though it acts simply as a protective powder with perhaps some astringent properties. It has been found that when swallowed it is at first deposited in the most dependent part of the stomach, but is later distributed evenly over the surface and forms a continuous sheet over any ulceration, which it thus protects from mechanical injury from the food, and also from the chemical action of the gastric juice. The subnitrate is the only one of the official preparations largely used for this purpose, and is generally administered in quantities of 2–3 G. (30–45 grs.) per day in powder. Recently the use of much larger quantities (10–15 G., 150–250 grs., per day) has been recommended. Bismuth has also been used in diarrhœa for its astringent and protective action on the intestine, which is again due to its being deposited on the mucous membrane and acting as a mechanical coating over irritated surfaces.

The subnitrate has been advised in surgery as an antiseptic, astringent powder to replace iodoform. It is true that it is devoid of the

[illegible]

irritant". Astringent taste, (sweetish) G.I. irrit but no poison [illegible] as chief thing needed

OK for kitchen utensils.

disagreeable odor of the latter, but it is not a harmless remedy, as was at first supposed, for several cases of bismuth poisoning have been recorded from its surgical use. Like iodoform, its value depends not so much on its germicidal action as on its absorption of the fluids of the wound, which renders the surface less suitable for the growth of bacteria. The therapeutic uses of the bismuth preparations then are largely due to their insolubility. The subnitrate is generally used, the carbonate less frequently, while the soluble double citrate is quite superfluous.

Several new compounds of bismuth have been introduced in therapeutics of late years, chiefly with the intention of combining the astringent properties of bismuth with the antiseptic action of benzol preparations. Among these may be mentioned the *salicylate* and *benzoate*, which have been used as intestinal antiseptics and astringents. Others are *airol* (bismuth oxyiodide gallate), *thioform* (bismuth dithio-salicylate), *bismuth phenolate, cresolate, orphol* (β-naphtolate), *xeroform* (tribromphenolate), *tannate, sulphocarbolate, dermol* (chrysophenate), *eudoxin* (tetraiodophenolphtaleinate). These have been used chiefly as cutaneous applications in various forms of skin disease, in which an astringent and protective powder is indicated, in burns and ulcers, in some ophthalmic conditions and as dusting powders after operations.

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like Beryllium

IX. ALUMINIUM AND ALUM.

The chief pharmacopœial preparation of aluminium is the sulphate of aluminium and potassium, or alum, which has been largely used for its astringent properties. Alum solutions precipitate albumin, but the precipitate is soluble in excess of the protein. It is not known whether an albuminate is formed similar to those of the heavy metals, though it seems probable that this is the case. Dilute solutions of alum have an astringent effect from their throwing down a layer of precipitated protein on the surface of the mucous membranes or on wounded surfaces, but larger quantities and more concentrated solutions act as irritants. This is more especially the case when dried alum is applied, for, in addition to its coagulating effect on the proteins, this preparation has a great avidity for water.

Symptoms.—Alum solutions have a sweetish, astringent taste, and in small quantities induce no symptoms except a feeling of dryness and astringency of the mouth and throat, and some constipation. Larger doses act as gastric irritants and cause nausea and vomiting, and, in extreme cases, purging. Even the largest quantities, however, are followed by no symptoms except those of gastro-intestinal irritation and inflammation, and the long-continued use of alum does not elicit any symptoms of chronic poisoning. The aluminium salts are

Acetate, chloride etc more antiseptic than boric acid.
General action (injected) – bowel, kidney, + brain.

not absorbed in any quantity from the stomach and intestine, so that no symptoms of general poisoning arise from the internal use of the salt. Aluminium vessels may be used for cooking, or even to contain acids, without danger of intoxication, as has been shown by a recent series of investigations.

Aluminium salts, especially the acetate, chloride and some more recent preparations, have very considerable antiseptic power, much more than some of the more generally used antiseptics, such as boric acid.

Action.—Aluminium has a very remarkable general action when it obtains access to the blood. In Siem's experiments on animals, the sodium-aluminium lactate or tartrate induced a very slow intoxication, mammals never dying from the effects sooner than one or two weeks after the intravenous injection of the salts. In frogs the symptoms were those of a descending paralysis of the central nervous system, the heart and the peripheral nerves and muscles being little affected. In mammals the first symptoms appeared only after three to five days, and consisted in constipation, rapid loss of weight, weakness, torpor and vomiting; marked abnormalities in movement and sensation were observed later, such as tremor, jerking movements, clonic convulsions, paresis of the hind legs, anæsthesia of the mouth and throat, and lessened sensation all over the body. Before death, diarrhœa often set in, and albuminuria was generally present. The mucous membrane of the stomach and bowel was found swollen and congested, the kidney and liver had often undergone fatty degeneration, and hæmorrhages were found in the renal cortex. Aluminium was found in the urine.

Like the other members of the heavy metal series, aluminium therefore acts on the bowel and kidney in general poisoning, while many of the symptoms point to a direct action on the brain. Döllken has recently confirmed Siem's results and showed that the nerve cells and fibres of the cord and medulla undergo degeneration, particularly those of the lower cranial nerves.

It has been stated that the alum salts of the food are absorbed and stored in the bones, but this is incorrect. What little is absorbed is probably rapidly excreted by the bowel and perhaps by the kidney.

A metal which is very nearly related to aluminium in its effects in the organism is Beryllium. It differs chiefly in being more poisonous, in being absorbed from the stomach and intestine, and in causing more distinct lesions in these when it is injected into the blood.

PREPARATIONS.

ALUMEN (U. S. P., B. P.), alum, potassium alum, ($AlK(SO_4)_2 + 12H_2O$), large, colorless, octahedral crystals, with a sweetish, strongly astringent taste, soluble in water, but not in alcohol. 0.3–1 G. (5–15 grs.). .3-1 Gs

Glycerinum Aluminis (B. P.), 10 per cent.

Alumen Exsiccatum (U. S. P.), *Alumen Ustum* (B. P.), burnt alum, dried alum ($AlK(SO_4)_2$), a white, granular powder, attracting moisture on exposure to air, soluble in water.

Alumini Hydroxidum (U. S. P.) ($Al(OH)_3$), a white, light, amorphous powder, odorless, tasteless, insoluble in water or alcohol, but soluble in hydrochloric or sulphuric acid and in fixed alkalies.

Alumini Sulphas (U. S. P.) ($Al_2(SO_4)_3$), a white, crystalline powder, with a sweetish, astringent taste, soluble in water, not in alcohol.

Uses.—Alum is used chiefly externally for its astringent properties. It has been employed as an emetic, but is less reliable than the sul-

[illegible] as astringent. Alum 1-5% - astringent gargle. ½-1% gonorrhea 1% lotion in skin diseases. Alum (dry) take H_2O, so caustic. Successful in chronic Pb poisoning

phate of copper or tartar emetic, and very large doses (4–8 G., 1–2 drs.) are required. In diarrhœa either alum or the hydrate is sometimes advised.

Alum solution is useful as an astringent gargle (1–5 per cent.), as an injection in gonorrhœa (½–1 per cent.), as an astringent lotion in skin diseases (1 per cent.), and for other similar purposes. Dried alum is more caustic, from its withdrawing fluid from the tissues. It has been used to a limited extent as an emetic; more frequently as an application to exuberant granulations, hæmorrhoids, or condylomata, and as a styptic in bleeding from the nose or teeth. Alum has often been prescribed in chronic lead poisoning with success. A solution (1 per cent.) has been injected into the rectum in chronic dysentery, but is inferior to the nitrate of silver.

A large number of aluminium preparations have been introduced recently as antiseptic astringents. Among these may be mentioned ***alumnol*** (naphtol sulphonate of aluminium), ***salumin*** (salicylate), ***tannal*** (tannate), ***gallal*** (gallate), ***boral*** (borotartrate), ***cutol*** (borotannate), ***alsol*** (acetate), ***alkasal*** (salicylate of potassium and aluminium). They are used partly in solution, chiefly as dusting powders.

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X. MINOR METALS.

Gold.

Gold has never been largely used in therapeutics, although repeated attempts have been made to introduce it in the treatment of the most diverse conditions; the salt employed has almost invariably been the double chloride of gold and sodium. It is much less poisonous than many of the other metals, and may be taken for many months without entailing any untoward symptoms. The subcutaneous injection in frogs is followed by paralysis of the central nervous system, gold possessing little action on the heart and striated muscles in these animals. Injected intravenously in dogs, it causes vomiting and dyspnœa, which soon pass off, but if sufficient has been injected the animal suffers from nausea, vomiting and diarrhœa for several days, eats nothing, loses flesh rapidly, and dies a week or more after the experiment. Numerous ulcers are found in the stomach and intestine, and these often betray their presence in life by hæmorrhages. Gold lowers the blood pressure somewhat on intravenous injection, probably from the dilatation of the mesenteric vessels accompanying the intestinal action. It has little effect on the rate of the heart except in large doses, and dilates the vessels when perfused through them. When given by the mouth to dogs and cats, it is at once ejected from the stomach by vomiting.

Gold has therefore the ordinary general effects of the heavy metals in causing acute irritation and ulceration of the alimentary canal. The early vomiting may be due to action on the centre, but is more probably caused by its irritating the stomach. The diarrhœa and the ulceration of the stomach and intestine probably indicate that it is excreted by these organs.

Gold has been used in various nervous disorders, in particular in those of a hysterical nature, and may conceivably be of value through suggestion, if the patient be informed of the nature of the remedy. Of late years it has been widely advertised as a specific in chronic alcoholism, but analysis has shown that no gold was contained in the fluid advocated, and there is no reason to suppose that it is of value except by means of suggestion.

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Platinum.

Platinum resembles gold in its action very closely, but is much more poisonous. In the frog it paralyzes the central nervous system and later the striated muscles. Kebler observed a stage of convulsions precede that of paralysis, the spasms evidently arising from the spinal cord or medulla oblongata. In mammals the symptoms resemble those of gold poisoning in almost every detail. Small quantities of platinum double salts injected intravenously increase the urine to some extent; larger injections cause albuminuria.

Platinum, like gold, was at one time advised in syphilis, but has never been widely used.

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Chromium.

Chromium is used in medicine in the form of chromic acid and the bichromate of potassium, which are both powerful oxidizing bodies in addition to their poisonous action as metallic oxides. The former property renders them more irritant and corrosive than most of the salts of the heavy metals. Chromic acid in particular is a powerful caustic, combining the action of a metallic oxide, an acid and a strongly oxidizing agent. Applied to the skin in substance it corrodes it, but is said to cause less pain than the more penetrating caustic potash. Even in dilute solution, the chromic salts and the acid act as skin irritants, and the caustic effects are shown by skin diseases, and particularly by deep, perforating ulcers in persons exposed constantly to the dust of chromic salts in factories. These ulcers arise from any abrasion of the skin, and the cartilaginous septum of the nose is also a common seat of ulceration, which eventually leads to perforation. They are due to the local action of the poison and not to its absorption; they are said to be almost painless. The inhalation of the dust leads to chronic bronchitis, while that swallowed and absorbed may give rise to nephritis.

Symptoms.—In acute poisoning, when a large quantity of the acid or of a salt is swallowed, the symptoms are those of gastro-intestinal corrosion, intense pain in the throat and stomach, vomiting and purging, with blood in the vomited matter and the stools, collapse and frequently death. The mouth and throat are stained yellow, and the stomach and intestine exhibit the usual appearance of violent corrosive poisoning.

The general action of chromic preparations may be elicited in animals by subcutaneous or intravenous injection, or by the administration of smaller quantities by the mouth. The symptoms resemble those caused by the general action of other metals. In the frog increasing weakness, tremor and eventually paralysis of the central nervous system are induced. In the mammal weakness and slowness in the movements is followed by albuminuria, glycosuria, diarrhœa and vomiting. Sometimes twitching of the muscles or even convulsions are seen, and then the weakness passes into general paralysis. The heart seems little affected by chromium, but the blood-pressure falls. After death the stomach and bowel are found congested, and the mucous membrane is necrosed and ulcerated in some parts, covered with ecchymoses in others. Hæmorrhages are also found in other organs of the body, notably in the heart wall. The kidney is in a state of acute parenchymatous nephritis and often contains deposits of uric acid and albumin, casts, and often blood cells appear in the urine. In chronic poisoning interstitial nephritis is said to occur.

Chromic acid and its salts are readily absorbed from the stomach and intestine. They seem to be excreted for the most part through the kidney, to a less extent by the intestinal epithelium probably. In the urine the metal occurs in part in organic combinations.

Chromic oxide compounds act in the same way as the chromate, but are much less poisonous.

PREPARATIONS.

Acidum Chromicum (B. P.), *Chromii Trioxidum* (U. S. P.), chromic acid or anhydride (CrO_3), forms crystals of dark purplish-red color and metallic lustre, odorless, very soluble in water. When brought in contact with organic substances, such as alcohol, glycerin or sugar, it oxidizes them rapidly and often violently with explosion.

Liquor Acidi Chromici (B. P.), 25 per cent.

Potassi Bichromas (B. P.), *Potassii Dichromas* (U. S. P.), bichromate or dichromate of potassium ($K_2Cr_2O_7$), forms large, orange-red transparent crystals, with a bitter metallic taste, soluble in ten parts of water. 6–12 mgs. ($\frac{1}{10}$–$\frac{1}{5}$ gr.).

Chromic acid is used as a caustic application to malignant growths, chancres and diphtheritic membranes, to a less extent as an irritant antiseptic. It has generally been applied by dipping a glass rod into a solution formed by allowing the crystals to deliquesce, or it may be fused on the end of a wire. It has also been advised in 5 per cent. solution as an application to prevent perspiration of the feet and to harden the skin.

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Manganese.

Traces of manganese are found in the blood and tissues of man and animals very frequently, but this metal is not an essential constituent of the body, but is apparently absorbed accidentally with the food. The salts of manganese in large quantities cause acute irritation of the stomach and intestine, like those of the other heavy metals, but no symptoms pointing to effects from the absorption of the metal are observed even when the administration is continued for a long time.[1] Manganese is absorbed from the alimentary tract, however, but only in very small quantity, and it appears to resemble iron closely in its course through the tissues (see page 660). Its general action has been elicited by the hypodermic or intravenous injection of double salts. In frogs manganese injected hypodermically causes a descending paralysis of the brain and spinal cord, and later weakens and arrests the heart, while the peripheral muscles and nerves seem unaffected. In mammals large injections induce epileptiform convulsions, particularly in the rabbit and guinea-pig. Smaller quantities, which cause a less acute intoxication, induce in the dog nausea and vomiting, diarrhœa, weakness, somnolence, stupor and death from arrest of the respiration. The urine is often increased, and contains bile pigment, and, towards death, albumin and casts. The stomach and bowel present no congestion or ulceration in these cases. Manganese is found in the vomited matter and the stools, in the liver, kidney and intestinal wall, to a less extent in the other organs. In acute poisoning in mammals the blood-pressure falls, from depression and paralysis of the vasomotor centre, while the heart is affected only much later. In subacute poisoning the darker color of the urine indicates icterus, but this is much more marked when small quantities are repeatedly injected into the subcutaneous tissues, and chronic poisoning induced. In chronic cases the nephritis, which is shown in the acute poisoning by albuminuria, is also more developed, the inflammation commencing in the secretory cells of the kidney but later involving the interstitial tissue, if the animal lives long enough.

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[1] Symptoms ascribed to chronic poisoning have recently been described by Embden as occurring in workmen in manganese.

Manganese injected hypodermically or subcutaneously is excreted chiefly by the intestinal epithelium, to a less extent by the kidney.

PREPARATIONS.

Mangani Dioxidum Præcipitatum (U. S. P.). Dose, 0.25 G. (4 grs.).

Mangani Sulphas (U. S. P.) ($MnSO_4 + 4H_2O$), colorless, or pale rose-colored crystals with a somewhat bitter, astringent taste, soluble in water, not in alcohol. 0.25 G. (4 grs.).

Mangani Hypophosphis (U. S. P.) ($Mn(PH_2O_2)_2$). 0.2 G. (3 grs.).

Manganese has been advised in chlorosis and especially in amenorrhœa, in which it is believed by many to have a specific action, while others have found it of no value in either of these conditions. In amenorrhœa the permanganate of potassium is generally prescribed instead of the dioxide or sulphate, but as it is at once reduced in the stomach, the effect is the same as if pure dioxide was administered.

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Cadmium resembles zinc very closely in its effects.

Nickel and **Cobalt** salts, administered to the frog, cause a curious dark color in the skin, followed by convulsive movements, which at first arise apparently from the medulla oblongata and higher centres, and resemble those of picrotoxin, but later are reflex, from excessive irritability of the spinal cord. In mammals the usual symptoms arising from the action on the intestine and kidney are accompanied by tremors and chorea-like movements, later by tetanus, and finally by paralysis. These metals also cause a profound fall in blood pressure resembling that from arsenic and apparently arising from direct action on the walls of the arterioles and capillaries. Strongly acid food may form nickel salts when it is cooked in vessels made of this metal, but no poisoning results, either because the quantity ingested is too small or because it is slowly absorbed from the stomach and intestine. Cobalt nitrate has been recommended as an antidote in prussic acid poisoning, as it forms an insoluble cyanide, but appears to be of little or no value; the oxide has been applied externally as an astringent, antiseptic powder.

Tin salts paralyze the central nervous system in the frog, and later the heart. In mammals diarrhœa, colic, vomiting and general weakness are observed, along with paralysis of some parts of the central nervous system and stimulation of others, leading to ataxia, stiffness and irregularity of the movements, and occasionally convulsions. The sulphide is said to be deposited in the lymph spaces of the intestines in the same way as in bismuth poisoning. General poisoning may be induced by the administration of the salts by the mouth, even when there is no corrosion of the mucous membrane. Tin is often contained in preserved foods containing acids, from being dissolved off the vessels, and is certainly absorbed, for it has been detected in the urine after the use of such articles. Apparently it is not often present in sufficient quantities to induce poisoning, for although some cases of "tin poisoning" are met with in medical literature, in none of them has it been satisfactorily established that tin was the cause. Chronic poisoning from this cause is unknown, and animals present no symptoms from prolonged treatment with larger quantities of tin than are contained in any preserved foods.

Thallium salts seem to resemble those of lead in their effects, but have a powerful depressant action on the heart, and are said to be more poisonous. Richet states that the injection of thallium acetate in animals is followed by a general atrophy of the muscles, especially of those of the jaw and spine, while baldness has followed its continued use in man.

Vanadium presents only the ordinary characteristics of metallic poisoning. The different oxides vary in toxicity, the pyrovanadates being much the most powerful.

Molybdenum and **Tungsten** resemble each other closely and induce typical metallic poisoning.

Uranium, in addition to the ordinary features of metallic intoxication, causes some glycosuria, the sugar often amounting to 1 per cent. in the urine. In addition, dropsy occurs in animals poisoned with this metal, partly from the changes in the kidney, but chiefly, it is said, from a destructive effect on the smaller vessels.

Selenium and **Tellurium** are classed along with sulphur in chemical systems, but the salts of telluric, selenious and selenic acid induce symptoms resembling those of the heavy metals and arsenic in many points, and may be inserted in this series. In the frog the symptoms are those of central nervous paralysis, and later of heart failure. In mammals vomiting, purging, somnolence, dyspnœa, tonic and clonic convulsions have been noted, and the stomach is found somewhat reddened, the mucous membrane of the intestine swollen and dysenteric, while the kidneys seem less affected. The perspiration is prevented by tellurates, apparently from a paralysis of the terminations of the secretory nerves similar to that induced by atropine. An early symptom of poisoning with these bodies is a garlic odor in the breath, and many of the organs are found of a grayish color after death, and possess this odor. Hofmeister has shown that these salts are reduced to metallic selenium and tellurium in the body, and that afterwards methyl compounds ($Te(CH_3)_2$, $Se(CH_3)_2$) are formed. These are volatile, and, excreted by the lungs, urine and fæces, give the disagreeable odor. The synthesis of methyl-tellurium is one of the few known cases in which a compound with methyl is formed in the animal body, and is of great biological importance. All the selenium and tellurium is not excreted in this form, for some of it appears in the urine, and probably in the fæces, in other combinations.

Tellurates have been advised in therapeutics to prevent excessive sweating, and certainly have this effect, but are not to be recommended, as the strong garlic odor of the breath persists for days or even weeks after one dose.

Osmic Acid has been recommended as an injection into the nerves in neuralgia. It is an intensely irritant substance, and seems to induce nephritis and diarrhœa when absorbed. The greater part of the poison is, however, deposited as a black powder at the point of injection, owing to its being reduced by the tissues.

Cerium was formerly used in therapeutics in the sickness of pregnancy and similar conditions, but is valueless. The cerium double salts injected into the blood vessels of animals are said to depress the heart and cause ecchymoses in the stomach and bowel, and nephritis. The oxalate is insoluble and is not absorbed from the alimentary tract.

Thorium is a very inactive metal, which does not seem to be absorbed from the alimentary tract.

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PART V.

FERMENTS, SECRETIONS AND TOXALBUMINS.

I. DIGESTIVE FERMENTS.

A NUMBER of digestive ferments have been introduced into therapeutics for the treatment of gastric and intestinal disorders. The earlier members of the series were proteolytic ferments, intended to reinforce the pepsin of the stomach, but of recent years the amylolytic ferments have also been strongly advocated.

Pepsin.

The pharmacopœial preparations of pepsin are generally obtained from the pig's stomach. It digests only in acid solution, the best results being obtained in a solution of 0.2 per cent. of hydrochloric acid. In alkaline solution it is inert, and in fact is rapidly decomposed, so that when pepsin and alkaline carbonates or bicarbonates are prescribed together, the effects are due to the alkalies only.

Pepsin is used in therapeutics on the theory that the stomach does not secrete enough of the ferment in certain conditions. But it may be questioned whether this is true in even a small proportion of the cases treated with pepsin, for the gastric juice is almost always capable of digesting proteins if it is acid in reaction. In a number of forms of dyspepsia the acid secretion is insufficient, but the ferment is almost always present in quantity, for it digests proteins outside the body as soon as it is acidulated. Pepsin is indicated then only in the rare cases in which the contents of the stomach acidulated with hydrochloric acid fail to digest proteins. It is very often administered in other forms of dyspepsia, and certainly does no harm, but there is no question that it is entirely unnecessary in the great majority of the cases in which it is prescribed.

PREPARATIONS.

Pepsinum (U. S. P., B. P.), a proteolytic ferment obtained from the glandular layer of fresh stomachs from healthy pigs, and capable of digesting not less than 3,000 times its own weight of freshly coagulated egg albumin.[1] It is a fine, white, amorphous powder or thin scales, free from offensive odor and having a mildly acid or saline taste, usually followed by a suggestion of bitterness. It is soluble in about 100 parts of water, but is more soluble if the water is acidulated. 0.2–0.6 G. (3–10 grs.), in powder, or in solution in 0.2 per cent. hydrochloric acid.

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[1] The B. P. preparation may be obtained from the pig, sheep or calf and is required to digest 2,500 times its weight of hard-boiled white of egg.

Pepsin is generally given during or after meals. As has been stated, it is very rarely indicated, as the gastric juice almost always contains sufficient ferment.

Glycerinum Pepsini (B. P.) contains hydrochloric acid. A fluid drachm represents 5 grs. of pepsin. 1–2 fl. drs.

Many other preparations of pepsin are used in popular medicine, to a less extent by the profession. Pepsin wines, for example, are often taken as tonics and digestives, but the wine is probably of greater efficacy than the ferment. In these pepsin wines the ferment is not destroyed, however, as is sometimes stated, for pepsin is able to digest proteins in much stronger alcoholic solutions than they represent.

Pancreatic Ferments.

The pancreatic ferments have also been introduced into therapeutics, generally in the form of an extract of the gland, *pancreatin*. These ferments differ from pepsin in acting only in alkaline or neutral solution, and besides digesting proteins, form sugar from starch and saponify and emulsify fats. The pancreatic ferments are rendered inert by a comparatively short exposure to the acid gastric juice.

The value of pancreatin is even more problematical than that of pepsin, for though it would no doubt be valuable where the digestive ferments, particularly those of the pancreas, were deficient, this has not been shown to occur. On the other hand, the pancreatic ferments are certainly destroyed in passing through the stomach. It has been suggested, however, that they may act in the stomach, if they are given before or with the food, as the acid gastric juice is only secreted slowly, and some time must elapse before the pancreatin is rendered inert. In cases in which there is a deficiency in the acid of the gastric juice, the pancreatin might conceivably act throughout the stay of the food in the stomach. Attempts have been made to preserve the pancreatin from the deleterious effects of the gastric juice by administering it in capsules which are dissolved only in the intestine. It is certainly possible that the pancreatin may be useful in certain cases, where the ferments of the pancreas are absent and the acid of the stomach so deficient as not to be destructive, but there is no reason to suppose that this series of accidents occurs at all frequently, and it is impossible to diagnose inefficiency of the pancreatic secretion.

PREPARATIONS.

Pancreatinum (U. S. P.), a mixture of the enzymes naturally existing in the pancreas of warm-blooded animals, usually obtained from the fresh pancreas of the pig. It forms a yellowish, yellowish-white, or grayish, amorphous powder, having a faint, not disagreeable odor and a meat-like taste, and is slowly soluble in water. 0.5 G. (8 grs.), in powder or in capsules. Keratin capsules have been proposed in order to protect the pancreatin from the gastric juice.

Liquor Pancreatis (B. P.), a liquid preparation containing the digestive principles of the fresh pancreas of the pig. The preparation is most active when the animal from which it has been obtained has been fed shortly before being killed. Two cubic centimetres of the solution ought to digest 80 c.c. of milk.

Benger's Liquor Pancreaticus is a solution of the pancreatic ferments made up with some alcohol.

In connection with the digestive ferments may be mentioned *ingluvin*, an extract of the fowl's gizzard, which was a few years ago highly recommended as a remedy in the sickness of pregnancy, but has proved entirely valueless.

Vegetable Ferments.

Besides these animal digestive ferments, a number of vegetable proteolytic enzymes are known, and have enjoyed a more or less short-lived popularity. Probably many more plant juices are able to digest proteids than are at present generally recognized; thus many of the bacteria liquefy gelatin and albumin, and the insectivorous plants, such as Drosera (sundew) and Dionea, secrete a digestive fluid. Figs, pine-apple (*bromelin*), the scarlet pimpernal (Anagallis arvensis), and many others of the higher plants have been shown to possess these ferments, but the best known of these is the Carica papaya, or pawpaw, which contains a digestive ferment known as *papain*, *papayotin* or *papoid*. This ferment acts in neutral, moderately acid, or alkaline solution at the temperature of the body and in the cold. It has been used instead of pancreatin and pepsin in disorders of the digestion, and also as an anthelmintic. Diphtheritic membranes have been treated by the frequent application of papain solution; the underlying disease was not favorably influenced, however, and the treatment has been abandoned. Papain solution has also been injected by the hypodermic needle into tumors and abscesses, with the intention of digesting the new growth, or accelerating the progress of the abscess towards the surface, but the results obtained do not encourage the further use of the remedy in this way. Peptones are unquestionably formed in the tumors when papain is injected.

Several milk-curdling ferments have been found in plants, but none of them have been used in therapeutics.

Diastase.

Several amylolytic or sugar-forming ferments have been used more or less in therapeutics, the first of these being the *diastase* or *enzyme of malt*, which is known under the names of malt extract, maltzyme, maltine, etc. When grain is allowed to germinate, its starch is formed into a soluble form (sugar) by means of a ferment known as diastase, and it was supposed that this diastase might aid the digestion of starchy foods in the body. When malt extract is formed at a low temperature, it unquestionably contains diastase and is capable of digesting starch, but many of the extracts on the market are quite inert, the ferment having been destroyed by heat. Those extracts are therefore devoid of digestive power, but form a pleasant, easily digested food. They often contain alcohol, and are then indistinguishable from beer or stout. More recently, some other sugar-forming ferments have been brought forward, notably that obtained from Eurotium oryzæ, a mould of the aspergillus family. This enzyme is known as *taka-diastase* from the name of its discoverer, Takamine, and is more powerful than any of the malt extracts. Taka-diastase has been recommended in cases in which there is supposed to be a deficient digestion of starch. It ceases to act in the gastric juice as soon as the acidity exceeds 0.1 per cent., but may be able to digest a certain amount of starch in the mouth and stomach before it is destroyed. The question at once arises, however, whether the ordinary digestive juices are ever unable to digest the starch of the food. And although a new term, "amylaceous dyspepsia," has been introduced to indicate this class of cases, if they should be found to exist, it must be admitted that no satisfactory evidence of their existence has been brought forward as yet. It is stated that more starch is found to be digested in the stomach after the administration of diastase, but this seems to be beside the point, for it merely indicates that less starch reaches the intestine for the pancreatic juice to act upon. Until it is shown that in some cases the digestion of starch by the intestinal ferments is insufficiently performed, the diastase preparations would seem to be superfluous.

II. BILE.

The bile is very seldom used in therapeutics at the present day, although it was formerly credited with great healing virtues. It has a bitter taste, and may have some effect like the vegetable bitters, but has no advantage over these, and is not likely to be used to promote the appetite now, although it was formerly used as a stomachic. The bile is found to precipitate the peptones in test-tube experiments, but does not appear to retard digestion in the stomach materially, judging from experiments carried out in a case of gastric fistula. In the intestine it is generally believed to act as an antiseptic, chiefly because the stools have a strong putrefactive odor in cases of retention of bile. Limbourg has also shown that the addition of bile to protein solutions delays their decomposition, while there is some evidence that it promotes pancreatic digestion. It has some purgative action, as is shown by the obstinate constipation which often occurs when it is prevented from reaching the intestine; according to Stadelmann, the bile acids irritate the mucous membrane of the large bowel and thus induce purgation. An obscure relation exists between the drastic purgatives and the bile in the intestine, several of them failing to act in its absence. (See page 99.) Bile increases the activity of the fat-splitting ferment of the pancreas and thus augments the absorption of fats. Most of the bile given by the mouth is absorbed in the stomach and small intestine and carried to the liver, which excretes it again, while a small quantity of the bile acids escapes in the urine. In the liver it increases the secretion of both the fluid and the solids of the bile; in fact, the bile is the only reliable cholagogue known. The constituent which acts on the secretory liver cells seems to be the bile acids, and their increase is greater than can be accounted for merely by the excretion of that administered, so that it would seem that they exercise some specific stimulant action on the secretory cells. The bile pigment is also augmented when bile acids are absorbed, owing to the destruction of the red cells of the blood, as the liberated hæmoglobin is carried to the liver and there formed into bile pigment.

Bile given by the mouth does not cause any symptoms except those from the intestine and liver. When it is injected into the blood, however, it depresses the central nervous system and the heart muscle from its direct action on these organs, and decomposes the red cells of the blood. Muscles and nerves suspended in a solution of bile salts rapidly lose their irritability, and some unicellular organisms are killed and dissolved by them. The poisonous constituent of the bile seems to be the salts of the bile acids, but several authors have stated that the pigment is also active.

Fraser has recently discovered that the bile has considerable virtue as an antitoxin. Thus the bile of the venomous snakes acts as an antidote to their poison, and the bile of other animals has also some effect in this direction. This antitoxic action is apparently due to the presence in the bile of cholesterin, which forms a loose combination or solution with the toxins and retards their absorption into the cells. It is much more efficient when it is mixed with the poison before its application, than when it is injected after the bite. Frazer adds that the bile is also an antitoxin to other poisons, including those produced by the pathogenic microbes. Others have found that the bile of animals dying of an infectious disease (rinderpest) possesses some curative properties in other animals suffering from the same malady, this being explained by the excretion of the antitoxin in the bile.

Bile has been used as a purgative, and it has been particularly recommended in the form of an enema. It does not seem to be reliable, however, and presents no advantages over soaps and similar substances.

As a cholagogue it is without rival, but no condition is known in which an increase of the bile secretion is indicated, for though it has been proposed to expel gall-stones by raising the pressure in the gall-ducts by cholagogues, it is found that when the pressure is only slightly increased, the secretion is arrested. It is inconceivable that the small rise in pressure could force out an impacted gall-stone.

Bile might be used to aid the absorption of fats, particularly when it is deficient in the bowel; in a case of biliary fistula Joslin found that much less fat and nitrogenous food escaped in the stools when the patient was treated with bile pills, than when no treatment was adopted.

Preparations.

Fel Bovis (U. S. P.), ox gall, the fresh bile of the ox.

Fel Bovis Purificatum (U. S. P.), *Fel Bovinum Purificatum* (B. P.), is formed from the fresh bile by the addition of alcohol, filtration and evaporation to pillular consistency. The alcohol is added to remove the mucus of the bile. The pigments may be removed by filtering the watery solution through animal charcoal.

Bile is always prescribed in the form of pills made from the purified preparation. 0.3–1 G. (5–15 grs.).

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III. INTERNAL SECRETIONS.

Until very recently the only animal secretions recognized in therapeutics were the digestive ferments, the bile, and a few rarely used substances, such as musk. But within the last few years it has been shown that certain glands supply the blood constantly with substances which are necessary to the economy, and a deficiency in which leads to the gravest symptoms. The subject of internal secretion is still in its infancy, but therapeutics has already been enriched with at least two additions of unquestioned value, and may profit still more by the further exploration of this field. The chief objects of "organotherapeutics," or the treatment of disease with extracts of the glands of the body (animal extracts), has been to supply a deficiency of the normal secretion. And the brilliant results obtained by the use of thyroid extract (page 521) have encouraged anticipations that further advances may be made in this direction. The investigation of the extracts of the suprarenal gland (page 334) and pituitary body (page 340) have also shown that the animal organs contain bodies which may be utilized in medicine in the same way as the more familiar plant extracts, and there is no reason to doubt that further exploration of this field will also prove profitable. Advance in organotherapeutics is not, however, to be expected from the indiscriminate use of the gland extracts in every sort of disease, such as is too popular at present. Such progress as has been made hitherto in this field has been due to careful observation and experiment, and not to haphazard use of the hypodermic syringe.

The **Thymus Gland** has been found to contain minute quantities of an iodine compound, which may be identical with that of the thyroid. Svehla found that the injection of an extract into the veins caused considerable acceleration of the pulse with some depression of the blood-pressure. The acceleration was found to be due to direct action on the heart, the fall of the blood-pressure to paralysis of the vaso-constrictors. Very large quantities caused restlessness, collapse and death. Thymus extract has been advised in exophthalmic goitre, and is said to be of some value in a certain number of cases, but does not benefit most patients.

The excision of the **Pancreas** in animals is followed by the appearance of sugar in large quantity in the urine, and in many cases of diabetes in the human subject the pancreas is found diseased, so that this gland seems to secrete some substance which is required by the tissues to enable them to maintain the normal amount of sugar in the blood. Extract of pancreas has therefore been administered in diabetes, but as yet without satisfactory results.

Bone Marrow extract and **Spleen** extract have been given in pernicious anæmia in order to increase the number of the red cells, and many other extracts of organs have been proposed, often on the most extraordinary grounds. It was not to be expected that these extracts of brain, heart, liver, kidney, prostate and lung would prove of benefit in the diseases of these organs, and experience has shown that they may without exception be relegated to the realms of quackery.

One extract deserves mention on account of the attention is has attracted, and the influence it has had on the theory of organotherapeutics—the extract of the **Testicles.** The use of testicular extract was first recommended by Brown-Sequard in 1889, as having a general tonic effect. He was led to this conclusion by the consideration that the sexual power is diminished in advanced life and made the bold step from this, that one of the causes of the woes of old age is the diminution of the internal secretion of the testes; this elixir of youth might, however, be obtained by extracting the organs in various ways. It is surprising how widely this theory has been accepted, and with what zeal all sorts of preparations of the testicles and ovaries, including the unaltered human semen, have been used in therapeutics, and, it must be added in justice to the observers, in experiments upon themselves. While there is no question that the removal of these organs exercises an important influence on a number of organs and tissues, there are no sufficient grounds for believing that the testicular extract has any effect whatsoever except through hypnotic suggestion. Two investigators have recently attempted to demonstrate the increase in the muscular strength by means of the ergograph, but the results obtained by means of this instrument in other investigations have proved so deceptive that little weight is to be laid on their results. Loewy and Richter state that extract of testicle increases the oxidation in the tissues of male castrated animals, but not in normal male animals or in castrated females; extract of ovary (*oophorin*) has a similar effect on the castrated female.

Instead of the extract of testicle, *spermine,* an alkaloid found in the testicle chiefly, but also in a number of other organs, has been proposed by Poehl. According to this author, it is an important factor in the oxidation of the tissues, and a number of symptoms of disease are due to its being precipitated in the form of the phosphate and thus rendered inactive, this being especially liable to occur whenever the alkalinity of the blood is reduced in any way. Poehl's spermine has therefore been advised in a large number of diseases, and in fact is considered by some almost a panacea. His statements are not founded on any satisfactory experimental or clinical observations, and have met with little credence from experienced physicians. Spermine was at one time supposed to be identical with piperazine, but this has proved to be erroneous.

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IV. TOXINS AND ANTITOXINS.

The toxins are a series of poisons whose existence has been recognized only in recent years and whose character is still obscure, but they play an ever increasing part in medicine. They are found in animals and in some of the higher plants, and have proved to be the means by which many of the pathogenic micro-organisms act in the tissues. Their chemical characters are still disputed, and none of them have been isolated in an absolutely pure form, as no means has yet been found to separate them from the proteins of the cells in which they are produced. Many observers are disposed to regard them as of protein character, while others believe that they are of simpler composition and merely attached by physical or loose chemical bonds to the proteins which accompany them.

These toxins are amongst the most powerful poisons known, but when animals are treated with small and gradually increasing doses, they become insusceptible to amounts that would prove fatal to an untreated control animal, and finally withstand in some instances many hundred times the ordinarily fatal dose. This acquired **Immunity** at first sight resembles the tolerance acquired for morphine and other poisons, but is different in character. For in the latter case, the organism no longer reacts to the poison which has become one of its usual constituents, exactly as a fresh water organism may slowly be rendered tolerant to sea water, the salts of which are gradually added to the fresh water and come to form part of the normal environment of the organism. On the other hand, when immunity to a toxin is acquired, by repeated administration, the organism forms a new antagonistic substance known as *antitoxin,* which prevents the toxin from having any effect by forming a loose combination with it, which is innocuous. Ehrlich has attempted to explain the formation of antitoxin in his well-known side-chain hypothesis by supposing that toxins combine with certain components of the living cells and that the organism reacts by forming those components in excess and freeing them in the blood serum, but much remains to be done before a clear picture of the process can be presented. In any case, the organism forms these antidotal substances far in excess of what is necessary to neutralize the quantity of toxin administered. And this excess can be obtained by bleeding the immune animal and collecting the serum; and when injected into an untreated animal this antitoxic serum lends it a certain degree of immunity to the subsequent injection of the original toxin. The use of this antitoxic serum may thus protect animals from the toxin of a disease, provided it be administered early. After the toxin is formed in the tissues, antitoxin is of less benefit owing to the damage already done, and the later the antitoxin is employed the less beneficial action it has. Each antitoxic serum antagonizes only the toxin which has been employed in its production, and affects only the toxin and not the organism which may have produced it. For example, the antitoxin for diphtheria toxin has no influence on tetanus toxin and is powerless against the diphtheria bacillus, which grows readily in the antidiphtheritic serum. On the other hand diphtheria toxin has no effect in an animal protected by an efficient dose of the diphtheria antitoxin. Each toxin must thus be combatted by the corresponding antitoxin, and the infection is not antagonised, but only the poison produced by the organism.

The antitoxic sera are entirely devoid of action except as antidotes to the toxin, provided they are injected into animals of the same species as that from which they are obtained. In therapeutics, animal serum has to be employed in man, and occasionally this gives rise to the symptoms which are liable to arise when ordinary serum is injected into an animal of another species. These symptoms are chiefly skin eruptions, such as erythema and urticaria, fever, and rheumatic pains in the joints and muscles, and, though unpleasant and sometimes alarming, have no serious results. They are not due to the antitoxin as such but to other constituents of the foreign serum, and are equally liable to arise when animal serum devoid of any antitoxic action is injected into man.

Apart from their action on the toxins, serums may also be specifically bactericidal, destroying or retarding the growth of the bacillus while affecting the toxin to a less extent. But these may be better treated of in connection with the microbes on which they act and by which they are formed.

Antidiphtheritic Serum.

When a horse is treated with injections of gradually increasing doses of diphtheria toxin, it acquires immunity to this poison, and its serum is found to neutralize the effects of large amounts of toxin injected into other animals. Blood is then drawn from the immunized horse, the serum is allowed to separate and is collected in sealed tubes; some antiseptic such as carbolic acid or cresol is added to preserve it. The amount of antitoxin in any serum must be ascertained, and this is done by animal experiment, the antitoxin unit being the amount necessary to protect an animal against 100 times the fatal dose of toxin for a guineapig of 250 G. weight. The antidiphtheritic serum is thus sent out standardized in units, some preparations containing 100 units in the c.c. and others as many as 300 or even 500 units.

SERUM ANTIDIPHTHERICUM (U. S. P.), Antidiphtheritic Serum, or Diphtheria Antitoxin, the serum of a horse immunized by the injection of diphtheria toxin, kept in sealed glass tubes in the dark and at a low temperature. It is a yellowish fluid, often slightly turbid, and with a slight odor of an antiseptic. Each tube bears a label giving the number of antitoxin units contained, the date at which the serum was tested, and the date beyond which it will have deteriorated appreciably. Average dose, 3,000 units; prophylactic dose, 500 units.

The use of this serum has revolutionized the treatment of diphtheria, and has reduced the mortality in this disease to about one-third or less of that prevailing before Behring introduced the method in 1893. The symptoms improve within 24 hours, the course of the disease is cut short, and there is not the fatal tendency to spread to new surfaces which was formerly seen. It is not yet determined how far the diphtheria paralysis is prevented by the serum. The remedy must be applied immediately, for when the tissues have been exposed to the toxin for some time the antitoxin has much less antidotal effect. For example, the prognosis is about four times as bad if antitoxin is injected on the third day as if it had been used on the second day of the disease. It is also effective as a prophylactic for those exposed to the infection. The antitoxin must be injected in large quantities, and it is desirable to have a serum containing a large number of units, because a weak serum can only be effective if injected in large doses, and these tend to induce skin eruptions and other unpleasant features. Only a few c.c. of a strong serum are necessary, and these do not contain enough of the foreign components to cause these symptoms.

Antidiphtheritic serum is a clear fluid in no way distinguishable from normal serum except by animal experiment. It often smells of phenol or cresol, which is added as a preservative. It slowly loses its antitoxin and should not be used if more than a year old. It is injected hypodermically, one thousand units in mild cases, and five thousand or more units in more severe cases and in those which are only treated several days after the infection. The same dose may be repeated after twenty-four hours if necessary.

Antitetanus Serum.

The tetanus bacillus forms a toxin which induces powerful tetanic spasms from an action on the spinal cord similar to that of strychnine. These may be elicited by the injection of the toxin and also arise from its absorption from wounds infected with the bacillus. An antitoxin is formed by immunizing horses in the same way as the antitoxin of diphtheria poison, and this injected into animals protects them from tetanus toxin. In tetanus infection from wounds, however, the toxin reaches the spinal cord, not through the lymph and bloodvessels, but by travelling along the nerve fibres, while the antitoxin circulates in the blood and reaches the nerve fibres and cells with difficulty (Meyer and Ransom). There is thus little opportunity for the neutralization of the toxin except that circulating in the blood, and the results of treatment with this serum are much less striking than those of the antidiphtheritic serum. But if the serum can be injected early, before the spinal cord has been attacked by the toxin, its effects are specific, and it is therefore used as a prophylactic in cases where tetanus infection is probable, and with the best results.

The antitetanus serum is standardized in the same way as the antidiphtheria serum and should not be used when more than a year old. It is injected in quantities containing 20–100 units, which may be repeated.

Antivenin.

The poisons secreted by the poisonous snakes contain toxins, and an antitoxic serum prepared by Calmette has been termed antivenine. It protects animals against a dose of snake poison which would otherwise be fatal and has also been used with success in snake bite in man. But the effects of snake bite manifest themselves so rapidly that there is not the same opportunity of using this serum as there is in the case of diphtheria. And the poison of different species of snakes varies in composition to some extent. When the antivenin is available, however, its injection should certainly form part of the treatment of snake bite.

Many other immune sera have been proposed, but as yet none of them have been generally accepted as of value.

Toxins are also found in a number of the higher plants.

Ricin is an intensely poisonous albumin found in the seeds of Ricinus communis along with castor oil, which does not itself contain this principle, however. Ricin is poisonous in doses of about $\frac{1}{25}$ milligram ($\frac{1}{1800}$ gr.) per kilogram body weight when it is injected into the blood, and is somewhat less poisonous when applied subcutaneously, but seldom causes any symptoms when swallowed, as it is apparently destroyed for the most part by the digestive ferments. It is thus among the most powerful of the vegetable poisons when it is injected directly into the blood. Death often occurs only several days after the injection in animals, and in the interval no symptoms make their appearance except some loss of appetite, and towards the end, diarrhœa and vomiting. Post-mortem, the bowel is found inflamed and congested and contains ecchymoses; blood is found in the serous cavities, and extravasations may occur in various other organs, although not so uniformly as in the bowel. Among the most obvious lesions are the innumerable ecchymoses in the great omentum and the swelling of the abdominal lymph-glands, which generally contain numerous small hæmorrhages. Microscopical examination reveals small foci of necrosed tissue in the liver, spleen, intestine, stomach and other organs. Ricin seems to be excreted by the intestinal epithelium, which may explain the violence of its action here, although it acts as a poison in many other tissues. It is a powerful irritant, inducing inflammation and suppuration when it is injected subcutaneously, or is applied to the conjunctiva. On the other hand it has little or no irritant action on the mouth and throat, and is digested and rendered harmless in the stomach. The mucous membrane of the nose is irritated by the inhalation of the powder in many persons. This toxalbumin has a very characteristic action on the blood. When a drop of a dilute solution is added to a test-tube of defibrinated blood, the corpuscles soon fall to the bottom, leaving the clear serum above, and the blood does not filter through paper any longer, the corpuscles all remaining on the filter, the serum passing through colorless. This is due to the agglutination of the red cells, which are formed into masses and thus fail to pass through the pores of the filter. Fibrin does not seem to be formed in the process, as was at one time supposed, but the nature of the cementing substance is unknown. Stillmark supposed that ricin formed these masses of red cells in the blood vessels, and that the symptoms were due to the emboli resulting, but this is certainly incorrect, for the blood of immune animals reacts in the same way, yet these are not poisoned by many times the usual fatal dose of ricin.

Ehrlich found that animals rapidly acquired immunity to the action of ricin, if they received for some time small non-toxic doses. From this discovery has arisen the whole of serum-therapeutics, which plays such an important rôle in medicine at the present time. By gradually increasing the daily amount of ricin, rabbits have attained an immunity of 5,000, that is, they are not affected by 5,000 times as much ricin as would have killed them had no preliminary treatment been instituted.

Ricin and its antitoxin are not used in therapeutics, but ricin has repeatedly given rise to poisoning, from the beans being taken as a substitute for the oil. Cattle have also been poisoned by being fed on the refuse of castor oil beans after the oil had been expressed.

Another vegetable toxin which resembles ricin very closely in its effects is **Abrin**, which is obtained from the seeds of Abrus precatorius or jequirity, the familiar scarlet and black beans, which are often formed into necklaces. Abrin contains two poisons, a globulin and an albumose, of which the former is the more powerful. It induces the same symptoms as ricin, but is less poisonous, and immunity can be acquired in the same way. Animals which are immune to ricin are not more resistant to the action of abrin than others, because the two poisons form different antitoxins. Abrin or jequirity has been used as an irritant to the eye in cases of granular lids and of corneal opacities. It causes an acute inflammation which improves the condition in some cases, but it must be regarded as an exceedingly dangerous remedy, as the inflammation is entirely beyond the control of the surgeon. In animals the eye is often completely destroyed by the application of abrin, while in other experiments enough of the drug is absorbed to cause fatal poisoning.

Crotin is another toxin, which is found in the Croton Tiglium, but which does not pass into croton oil. It is less poisonous than ricin and abrin, but resembles them in most other points, except that it does not cause agglutination of the blood cells of certain animals, while ricin and abrin have this effect in all kinds of blood hitherto examined.

V. COD-LIVER OIL.

Cod-liver oil has long been used by the fishermen of the North Sea as a remedy in children's diseases, and was introduced into medicine in the beginning of last century, but became generally used only in the last fifty years.

It is obtained from the liver of the cod-fish (Gadus morrhua), and probably from other members of the genus. Formerly the livers were left to decompose and the oil set free by the breaking up of the cells was collected. It had a most disagreeable odor and taste, however, and many patients could not be induced to take it, while those who were courageous enough to swallow it often suffered from eructation and diarrhœa afterwards. This method was therefore soon replaced by the "steam-process," in which the oil is melted out of the fresh livers, yielding an oil of much lighter color, and with much less disagreeable smell and taste. Quite recently a new process has been introduced by which the oil is extracted by steam, without being exposed to the air, and it is stated that oil thus obtained is less disagreeable than any other.

The cod-liver oils used in therapeutics differ considerably in appearance and in composition, the older preparations being brownish in color and having a strong fishy odor and a somewhat acrid, disagreeable taste, while the oil prepared by the more recent processes is pale yellow in color, and has much less odor and a bland taste.

Cod-liver oil, like the oils derived from the livers of other animals, contains the ordinary glycerin oleate, palmitate and stearate, and also glycerin esters of some unidentified non-saturated acids, along with lecithin. Some free fatty acid is generally found in it, the darker preparations containing some 4–7 per cent., the pale yellow oil less than 1 per cent. as a general rule.

Iodine and bromine are present in traces, apparently very much smaller in amount than is generally believed. The usual statement is that 0.03–0.04 per cent. of iodine and 0.003–0.005 of bromine exists in the oil, but some oils have been found to contain only about one-hundredth of this amount of iodine.

Phosphorus is found in traces in some oils, in an organic combination, not in the free state. A small percentage of cholesterin is often, not invariably, present, and bile acids and pigments have been said to occur, but this seems incorrect. A number of bases have been found in cod-liver oil by Gautier, especially in the darker colored varieties, while the pale yellow oil contains little or none.

Cod-liver oil has no very distinct action when taken in ordinary doses, while in large quantities it has a tendency to cause eructation, nausea and diarrhœa. Taken repeatedly, it increases the weight and strength and improves the general condition. The same effects are obtained in healthy persons by the use of good food and fats, but delicate patients who are unable to digest ordinary animal fats are able to take cod-liver oil. Its effects are obviously those of an easily assimilable food, and it is not a drug in the ordinary sense of the term, and has therefore no place in pharmacology properly speaking, but should be classed along with other foods. It is always treated of as a drug, however, because it has often been supposed to have some specific effect quite apart from ordinary foods. It is generally believed to differ from ordinary fats in being more readily assimilable, but the explanation of this fact is by no means agreed upon, for though it is often said to be more rapidly absorbed from the intestine, there is little reliable evidence that such is the case. A few experiments have been carried out, but by no means enough to establish the truth of the statement satisfactorily, and the chief argument brought forward in its support is that cod-liver oil forms an emulsion in the test-tube more rapidly than other oils. It is undoubtedly well borne by the stomach, but it has not been often compared with other oils in regard to this point, and it is still impossible to state that other oils administered with the same care as cod-liver oil are not equally successful remedies.

Buchheim explained that cod-liver oil formed an emulsion rapidly on account of the free acid it contained, and this has generally been put forward as accounting for its effects in therapeutics. As far as regards the old dark-colored oils, this explanation may hold good, but the pale oil now used in therapeutics often contains less free acid than ordinary olive oil. Some enthusiastic supporters of Buchheim's theory have therefore asserted that the pale oil does not give the same results as the older, less pure, acid preparations, but this is not the general opinion of the medical profession.

The older explanations started from the view that cod-liver oil is a drug, that the oil itself is only a means to administer certain active principles contained in it. Thus iodine and phosphorus were in turn supposed to be the essential constituents, but have both been shown to be present in too small quantities to be of any effect. More recently cholesterin has been suggested as the curative agent, but it is present in smaller quantities in cod-liver oil than in many other foods. The bases are apparently quite inactive in the quantities contained in the oil.

Several substitutes for cod-liver oil have been proposed, such as *Lipanin* (v. Mering), which is formed from olive oil by the addition of 6 per cent. of oleic acid, and which was suggested by the theory that cod-liver oil owes its rapid absorption to the presence of free acid. *Morrhuol,* a crude mixture of bases, acids and pigment, has been introduced into therapeutics and used to some extent, but it has not proved a substitute for the oil in practice.

On the whole, cod-liver oil has not been shown to have any action apart from that of an easily digested food, and its superiority to some other fats and oils has not been satisfactorily established.

PREPARATIONS.

OLEUM MORRHUÆ (U. S. P., B. P.), cod-liver oil, Oleum Jecoris Aselli, a fixed oil obtained from the fresh livers of Gadus Morrhua and of other species of Gadus—a pale yellow, thin, oily liquid, with a peculiar, slightly fishy, but not rancid odor, and a bland, slightly fishy taste. 4–16 c.c. (1–4 fl. drs.).

Emulsum Olei Morrhuæ (U. S. P.), 50 per cent. 8 c.c. (2 fl. drs.).

Emulsum Olei Morrhuæ cum Hypophosphitibus (U. S. P.), 50 per cent. cod-liver oil. 8 c.c. (2 fl. drs.).

Therapeutic Uses.—Cod-liver oil is used in chronic wasting diseases, such as tuberculosis, scrofula, rickets and some forms of syphilis. It is especially beneficial in the earlier stages of pulmonary phthisis, but has no specific virtues here or elsewhere apart from those of an easily digested fat. In all forms of malnutrition and delicacy in children it is largely used, and undoubtedly causes a considerable increase in weight, but care must be taken that it does not disturb the digestion, especially if the darker oils are used. In some persons pure cod-liver oil always induces nausea, but a much larger number refuse to take the brown oil. In most cases the light-colored oil is taken readily, especially if the dose be small at first (a teaspoonful). When there is dyspepsia or a tendency to diarrhœa, cod-liver oil should be given with caution, and it is generally prescribed only in cold weather, as it is found that patients have a distaste for it in summer. When fever or acute disease is present, cod-liver oil is generally found of little value, perhaps on account of the disturbed condition of the digestion. Cod-liver oil should not be forced on patients; when it continues to induce nausea and eructation after a fair trial, it should be abandoned.

Innumerable means have been proposed to conceal the odor and taste, but it is generally conceded that when possible the pure oil is better given alone. When patients cannot be induced to take it in this way, some volatile oil, ether, or brandy may be added to it; saccharine has also been used to sweeten it. Creosote is sometimes mixed with cod-liver oil in cases of phthisis, or an emulsion is formed containing cod-liver oil, some flavoring substance, iron, hypophosphites or calcium. Extract of malt and cod-liver oil form a common mixture, and are the basis of many patented emulsions.

In general, the pale oil is preferred, but it must be added that some physicians persist in the use of the darker forms, which contain more bases and more free acid, but have a much more disagreeable taste and smell, and are more liable to disturb the digestion. Of the substitutes for cod-liver oil, lipanin has little taste and is generally taken readily. It may be given shaken up in milk or formed into an emulsion.

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VI. PHLORIDZIN.[1]

Phloridzin is not used in therapeutics, but has attracted some attention from its effects in animals, and may therefore be mentioned shortly. It is a glucoside ($C_{21}H_{24}O_{10} + 2H_2O$) found in the rootbark of the apple, pear, cherry and plum tree. When given in large quantities by the mouth it sometimes causes some diarrhœa in animals, but apart from this its only effect is glycosuria, which also follows its injection subcutaneously or intravenously. The urine is found to contain 5–15 per cent. or even more of sugar, sometimes along with acetone and oxybutyric acid, so that the intoxication seems at first sight to resemble diabetes mellitus in man very closely. Phloridzin induces the same results in man and the glycosuria is not accompanied by any other symptoms generally. It differs from true diabetes, however, in the fact that the sugar of the blood is not increased in amount. The glycosuria is not due to any change in the general metabolism of the body, therefore, but to some alteration of the renal epithelium, by which the blood sugar escapes into the urine, instead of being retained in the body and used as a source of energy. This has been definitely proved by Zuntz, who showed that when phloridzin was injected into one renal artery, the urine secreted by the corresponding kidney contained sugar, while that from the other remained normal for some time. According to the most recent views, phloridzin enables the renal cells to form free sugar from some combination in the blood, and this free sugar then escapes in the urine. As the available sugar is drained off in the urine, the tissues rapidly manufacture more and pour it into the blood. As long as sufficient food is given, the loss of sugar does not seem to entail any increase in the destruction of the proteid tissues, but when phloridzin is given to starving dogs, the waste of sugar has to be made up from the tissues, and the nitrogen of the urine accordingly rises in amount, while at the same time the liver cells become infiltrated with fat globules. The statement that the sugar of the milk is increased by phloridzin has proved to be incorrect.

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[1] Phloridzin is not in any way related to the other drugs of this part, and has only been inserted here because no suitable position could be found elsewhere.

Glycosuria may be maintained for an indefinite time if the administration of phloridzin be continued, and animals recover rapidly when the treatment is stopped. The glucoside is probably excreted in the urine unchanged, although this has not been quite satisfactorily demonstrated as yet. Phloridzin may be decomposed into a sugar, phlorose, and phloretin, which also induces glycosuria.

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PART VI.

MENSTRUA AND MECHANICAL REMEDIES.

Oleum Theobromatis (U. S. P., B. P.), cacao-butter, a fixed oil expressed from the seeds of Theobroma cacao, forms a yellowish-white solid having a faint, agreeable odor and a bland, chocolate taste. It melts a little below the temperature of the body. Cacao-butter is used almost exclusively to form suppositories, in which astringents and other remedies are incorporated. When introduced into the rectum they melt and the active principle is liberated.

Keratin (not official) is a substance obtained from horns, hoofs, nails, etc., which is insoluble in the gastric juices, but is dissolved by the alkaline pancreatic secretion. It is used to coat pills which it is desired to protect from disintegration in the stomach.

Kaolinum (B. P., U. S. P.), or porcelain clay, is used in the formation of pills containing easily reduced bodies, such as silver nitrate or potassium permanganate. Mixed with the ordinary vegetable excipients, such as confection of roses, or extract of liquorice or gentian, these salts would be reduced at once. Kaolin is an aluminium silicate and forms a soft whitish powder insoluble in water or dilute acids.

Cataplasma Kaolini (U. S. P.), kaolin moistened with glycerin and applied as a poultice.

Sapo (U. S. P.), **Sapo Durus** (B. P.), hard soap, white Castile soap, is prepared from soda and olive oil.

Sapo Mollis (U. S. P., B. P.), soft soap, sapo viridis, a soap made from potash and olive oil.

Sapo Animalis (B. P.), curd soap, soap made with sodium hydroxide and a purified animal fat consisting chiefly of stearin; it contains about 30 per cent. of water.

These soaps are used in therapeutics as ingredients of liniments and plasters. Water containing soap is often thrown into the rectum as an enema, and in infants a soapstick inserted into the anus generally provokes evacuation of the bowels in a few minutes.

Soaps impregnated with antiseptics, such as perchloride of mercury, carbolic acid, tar, or iodine, are often used to disinfect the hands.

The chief preparations in which soap is used in the pharmacopœias are:

Emplastrum Saponis (U. S. P., B. P.), soap plaster.

Linimentum Saponis (U. S. P., B. P.), soap liniment.

Linimentum Saponis Mollis (U. S. P., B. P.).

The liniments consist of alcohol with soap in suspension, perfumed with volatile oils, and are mildly irritant to the skin. They are used largely as bases for other liniments.

The use of the oils, fats and glycerin as vehicles for the application of remedies to the skin has been mentioned already (page 48). They may also be used to dissolve remedies which are insoluble in water, but which are to be given by the mouth, such as phosphorus (in oil).

Wax (cera alba, cera flava) is used chiefly to increase the consistency of ointments. A special series of preparations somewhat stiffer than the ointments are the cerates of the U. S. P.

Plasters are sticky, adhesive substances which are chiefly used to give mechanical support, but which are often impregnated with active remedies in order to elicit their local action on the skin. The basis of many of the plasters is lead plaster, which is obtained by the action of lead oxide on olive oil and consists for the most part of lead oleate.

Emplastrum Plumbi (U. S. P., B. P.), lead or diachylon plaster.
Emplastrum Adhæsivum (U. S. P.), *Resinæ* (B. P.), adhesive plaster.
Emplastrum Saponis (U. S. P., B. P.), soap plaster.
Emplastrum Belladonnæ (U. S. P., B. P.), belladonna plaster.
Emplastrum Picis (B. P.), Burgundy pitch plaster.
Emplastrum Capsici (U. S. P.).
Emplastrum Calefaciens (B. P.), warming plaster.
Emplastrum Cantharidis (B. P.).
Emplastrum Hydrargyri (U. S. P., B. P.), mercury plaster.
Emplastrum Menthol (B. P.).

Court plaster is formed from isinglass, the dried swimming bladder of several species of sturgeon, which is dissolved in water, alcohol and glycerin and painted on taffeta. Isinglass differs from lead plaster and its derivatives in being transparent, so that if it be spread on a flesh-colored cloth, it disfigures the hands and face less than the others.

Lead plaster, adhesive plaster and isinglass plaster are used only to cover and protect cuts and abrasions, and to keep the edges of wounds in apposition. The adhesive plaster and isinglass plaster are superior to lead plaster, as they stick more firmly. It is perhaps unnecessary to add that plasters are always applied spread on cloth. Opium and belladonna plasters are believed to lessen pain locally as well as to give support, but this is perhaps imaginary. Belladonna plaster is said to lessen the secretion of perspiration and of milk. The pitch, arnica, menthol and capsicum plasters have some irritant action and this is of course more marked in the case of the warming plaster and cantharides plaster. Some mercury is absorbed when the mercury plasters are applied to the skin, but this method of administration allows of even less accurate dosage than inunction, and is seldom used.

Another series resembling the plasters in their sphere of usefulness is formed by the **Collodia.** Their basis is pyroxylin, or soluble gun-cotton, which is formed from cotton by the action of sulphuric and nitric acids, and which consists of a mixture of nitrates of cellulose. Collodion is formed by dissolving pyroxylin in a mixture of alcohol and ether. When these evaporate, there remains a fine layer of pyroxylin, which protects the surface to which it is applied and gums the edges of slight cuts together. This collodion is rendered less brittle by the addition of Canada turpentine and castor oil in small proportions, and is then known as flexible collodion. A blistering collodion is formed by the addition of powdered cantharides to the flexible preparation. Another preparation contains tannic acid.

Pyroxylinum (U. S. P., B. P.), soluble gun cotton, colloxylin.
Collodium (U. S. P., B. P.), collodion.
Collodium Flexile (U. S. P., B. P.), flexible collodion.
Collodium Cantharidatum (U. S. P.), *Collodium Vesicans* (B. P.), blistering collodion.
Collodium Stypticum (U. S. P.), contains 20 per cent. of tannic acid.

Instead of collodion, india-rubber, *Caoutchouc* (B. P.), *Elastica* (U. S. P.), may be dissolved in chloroform and applied in the same way.

Calcii Sulphas Exsiccatus (U. S. P.), Dried Gypsum, used to impregnate bandages, which then become hard and immovable.

CLASSIFICATION OF DRUGS ACCORDING TO THEIR THERAPEUTIC USE.

I. Drugs applied for their local action to the skin, wounds, or visible mucous membranes.

Corrosives or caustics.

Potash, 547
Mercury nitrate, 659
Potassium and sodium carbonate, 547
Silver nitrate, 688
Zinc chloride, 685
Nitric acid and other acids, 562
Chromic acid, 699
Burnt alum, 696
Bromine, 589
Arsenic, 608
Lead nitrate, 673
Trichloracetic acid, 570
Ammoniated mercury and other mercury preparations, 659
(Soda, 547)
(Sodium ethylate, 552)
(Lime, 571)
(Carbolic acid, 449)

Disinfectants and antiseptics.

Hydrogen peroxide, 593
Permanganate of potassium, 596
Chlorine, 589 } not applied to living objects.
Sulphurous anhydride, 569 } not applied to living objects.
Formaldehyde, 473 } not applied to living objects.
Carbolic acid, 449
Corrosive sublimate and other mercury salts, 656
Silver nitrate, 688
Zinc chloride, 685
Boracic acid, 585
Iodoform, Iodol, 517
Cresol, 455
Tar, 460
Salicylic acid, 463
(Benzoic acid, 473)
(Camphor, 69)
(Sulphites, 536)
(Sulphocarbolates, 473)
(Volatile oils (thymol, eucalyptol, etc.))

Astringents.

Tannic acid series, 111
Iron preparations, *e. g.*, sulphate, 660
Bismuth preparations, 693
Lead acetate, 673
Zinc sulphate and oxide, 685
Copper sulphate, 682
Alum, 696

Styptics.

Soluble astringents (see above).
  Iron perchloride, 660
  Silver nitrate, 688
  Burnt alum, 696

To contract vessels and reduce hemorrhage and swelling.

Cocaine, 304
Adrenaline, 334

Emollients or protectives.

Emollients, 48
Plasters and Collodia, 721
Dusting-powders—starch, talcum, chalk, and many insoluble metallic powders, which may also be slightly astringent, 52

Local anodynes and analgesics for pain and itching.

Bicarbonate of potassium, 547
Cocaine, Eucaine, Orthoform, etc., 304
Carbolic acid, 449
Chloretone, 195
(Prussic acid, 245)
(Atropine, 282)
(Aconite, 385)
(Veratrine, 391)

Local anæsthetics.

Cold by evaporation of ether, etc., 183
Cocaine and Eucaine, 304

II. Drugs used for affections of the alimentary tract.

- MOUTH AND THROAT (see Section I.).
  - *Demulcent*, 45
    - Chlorates, 529
    - Ammonium chloride, 498
    - Cubebs, 77
  - *To lessen salivation.*
    - Atropine, 282
  - *Flavoring substances.*
    - Sugars, 53
    - Volatile oil series, 58
    - Acids (citric), 571
    - Syrup of Tolu, Ginger, etc.
- STOMACH.
  - *Digestives.*
    - Pepsin, Papain, etc., 705
    - Hydrochloric acid, 567
  - *Emetics.*
    - Common salt, 488
    - Mustard, 91
    - Warm water.
    - Apomorphine, 240
    - Ipecacuanha, 396
    - Tartar emetic, 635
    - Copper sulphate, 682
    - Zinc sulphate, 685
    - (Alum, 696)
    - (Ammonium carbonate, 557)
  - *To lessen irritation and vomiting.*
    - Opium, 212
    - Chloral, 189
    - Lime-water, 571
    - Bismuth, 693
    - Cold (ice).
    - Cocaine, 304
    - Carbonic-acid water, 587
    - Demulcents, 45
    - (Prussic acid, 245)
  - *To lessen acidity, antacids.*
    - Potassium and Sodium carbonate and Bicarbonates, 547
    - Magnesia and Magnesium carbonate, 547
    - Lime-water and chalk, 571
    - Lithium carbonate, 547
  - *To increase secretion, bitters.*
    - Simple bitters, 54
    - Nux vomica, Strychnine, 198
    - Cinchona and Quinine, 409
    - (Hydrastis, 235)
    - (Salicin, 468)
  - *Carminatives.*
    - Volatile oil carminatives, 58
    - Alcoholic preparations.
    - Carbonic acid waters, 587
    - Carbonates and Bicarbonates, 547
    - Bitters (see above).
    - Camphor, 69
    - Charcoal, 584
    - Ammonium carbonate, 547
- INTESTINE.
  - *To promote digestion.*
    - (Pancreatin, 706)
    - (Diastase, 707)
  - *To promote evacuation—purgatives.*
    - Vegetable purgatives, 96
    - Saline cathartics, 538
    - Mercurial purgatives—Calomel and Metallic preparations, 640
    - Sulphur, 581
    - Enemata.
    - Glycerin suppositories, 51
    - (Atropine).
  - *To lessen movement and relax spasm.*
    - Opium and Morphine, 212
    - Tannic acid series, 111
    - Lime-water, 571
    - Lead acetate, 673
    - Bismuth, 693
    - Atropine (to relax spasm), 282
    - (Alum, 696)
  - *To destroy parasites—anthelmintics.*
    - Male fern, 118
    - Pomegranate, 121
    - Cusso, etc., 120
    - Santonin, 122
    - Calomel, 634
    - Salol, 467
    - Thymol, Naphtol, 455
    - (Some volatile oils).
    - (Chloroform, 155)
    - (Quassia enema, 54)
  - *Disinfectants and antiseptics.*
    - (Vegetable and Saline purgatives.)
    - Mercurial purges—Calomel, 640
    - Naphtol, 458
    - Salol, 467

III. Drugs used for their effects on the circulation.

HEART.

To strengthen contraction.
Digitalis group, 357

To accelerate pulse.
Atropine, 282
(Camphor, 69)
(Caffeine, 250)

To slow the pulse.
Digitalis group, 357
Aconite, 385
Veratrine, 391
(Strychnine, 198)

VESSELS.

To contract calibre and raise blood-pressure
Digitalis, 357
Strychnine, 198
Caffeine, 250
Camphor, 69
Ergot, 341
Adrenaline (intravenously), 334

To relax vessels and lower blood-pressure
Nitrite series, 349

To arrest internal hemorrhage (styptics).
Ergot, 341
Hydrastine and Hydrastinine, 235
Opium and Morphine (to allay restlessness).

To remove fluid (dropsy, anasarca).
Digitalis series, 357
Diuretics (see Kidney, below).
Saline cathartics, 538
Diaphoretics (see Skin, below).
(Vegetable cathartics, 96)
(Salicylic acid, 463)

IV. Drugs used for their effects on the genito-urinary system.

To increase the flow of urine (diuretics).
Caffeine and Theobromine, 250
Digitalis and Squills, 357
(Turpentine, Uva Ursi, Scoparius).
Nitrates, 534
Acetates, 557
Citrates, 557
Iodides of the alkalies, 508
Carbonates, 547
Mercury—calomel and blue pill, 640

To render the urine less acid.
Alkali carbonates and bicarbonates, 547
Acetates, 557
Citrates, 557

To render the urine antiseptic.
Copaiba series, 77
Salol and Salicylates, 463
Sodium sulphocarbolate, 473
Borax, 585
Urotropine, 480
Local antiseptics, astringents, anodynes, caustics, etc., are used in the urethra and bladder.

To promote contraction of the uterus (ecbolics).
Ergot, 341
Quinine, 409
(Pilocarpine, 318)
(Cottonroot-bark, 349)
(Hydrastis, 235)

To promote menstruation (emmenagogues).
Iron, 660
Aloes, 101
(Myrrh).

V. Drugs used for their effects on the respiratory system.

To stimulate the respiratory centre.
Atropine, 282
Caffeine, 250
Camphor, 69
Strychnine, 198
(Alcohol?).

To reduce the irritability of the centre in cough.
Opium, Morphine, and Codeine, 212
(Heroine).
Chloral series, 189
Bromides of the alkalies, 501

To increase and liquefy the bronchial secretion.
Ipecacuanha, 396
Tartar emetic, 635
Squills, 357

Senega, 403
Ammonium carbonate, 557
Iodides of the alkalies, 508
(Lobelia, 271)

To lessen the secretion of the bronchi (?).
Benzoic acid, Benzoin, Tolu Balsam, 473
Ammonium chloride, 498
(Cubebs, 77)

To relax bronchial spasm in asthma.
Belladonna and Atropine, 282
Lobelia, 271
Nitrite series, 349
Iodides, 508
(Charta potassii nitratis, 536)
(Aspidosperma, 408)

VI. Drugs used for their effects on the central nervous system.

Stimulants.
(*a*) *The spinal cord.*
Strychnine, 198
(*b*) *The brain and medulla oblongata.*
Atropine (cocaine), 282
Camphor, 69
Caffeine, 250

Depressants.
(*a*) *To paralyze sensation—General anæsthetics.*
Ether, Chloroform, Nitrous oxide, 155–189
(*b*) *To induce sleep and rest—hypnotics or narcotics.*
Opium and Morphine, 212
Alcohol, 131
Chloral group, 189
Bromides, 501
Hyoscine, 282
Cannabis indica, 237

To relieve pain—analgesics or anodynes.
Opium, 212
Cannabis, 237
Antipyrine series, 425
(Alcohol, 131)
(Chloral, 189)
(Arsenic, Iodides, Quinine, Nitrites are sometimes of value in headache).

VII. Drugs used to reduce fever temperature.

Antipyrine and Acetanilide group, 425
Quinine, 409
Aconite, 385
Salicylic acid group, 463
Diaphoretics (see below).
(Resorcin, Guaiacol, 456)

VIII. Drugs used for their effects on the liver.

To increase the secretion of bile—cholagogues.
Ox-gall, 708
(Salicylic acid, 463)

IX. Drugs used for their effects on the blood.

To increase the hæmoglobin.
Iron, 660
Arsenic, 608

To increase the alkalinity.
Alkali carbonate group, 547
Acetates and Citrates, 557

X. Drugs used for specified diseases.

In malaria.
Quinine, 409
Arsenic, 608
In syphilis.
Mercury, 640
Iodides, 508
In rheumatic fever.
Salicylates, Salol, 463
In myxœdema and some other thyroid diseases.
Thyroid extract, 521
In trypanosomiasis.
Arsenic (atoxyl), antimony, 621
In gout.
(Colchicum, 400)

XI. Drugs used for their effects on the skin.

Corrosives or caustics, 723
Emollients and protectives, 723
Local anodynes and anæsthetics, 723
Irritants.
Turpentine oil group, 88
Mustard, 91
Cantharides, 92
Croton oil, 100
Tartar emetic, 35
Camphor, 69
Menthol, 69
Iodine, 514
Ammonia, 557
(Aconite, 385)
(Veratrine, 391)

Disinfectant or irritant ointments in parasitic skin diseases.

Mercury ointment, 640
Sulphur ointment, 581
Tar, 460
Ichthyol, 463
Benzoin, Storax, and Peru balsam, 473
Naphtalin and Naphtol, 458
Resorcin, 456
Thymol, 455
Pyrogallol, 457
Chrysarobin, 105
Camphor, 69
Boracic acid, 585
Iodol and other organic iodine compounds, 521
Organic bismuth preparations, 693
Alum preparations, 696
Arsenic, Iodide of Potassium, etc., may be used internally in skin diseases.

Drugs administered internally to increase the secretion of perspiration (diaphoretics or sudorifics).

Ipecacuanha, 396
  and other nauseating expectorants (antimony).
Ipecacuanha and Opium (Dover's powder), 396
Camphor, 69
Pilocarpine, 318

Drugs administered internally to lessen secretion of perspiration.

Atropine and Belladonna, 282
Agaricin, 303
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